Administrative Document

Annual Report of the Addiction Research Center

National Institute on Drug Abuse

Fiscal Year 1987

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration
National Institute on Drug Abuse
5600 Fishers Lane
Rockville, MD 20857

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October 1, 1986 to September 30, 1987

Summary Statements and Individual Project Reports

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Jerome H. Jaffe, M.D., Director

This report on the Addiction Research Center (ARC) represents the progress during fiscal year 1987. During this fiscal year new resources available under the President's Drug Abuse Initiative made it possible to begin, for the first time in the ARC's 50 year history, outpatient studies on the treatment of drug abuse. Despite the new resources, the full personnel complement has not yet been recruited in some laboratories. These factors continue to be reflected in the very different levels of activity demonstrated by our various organizational components.

This year's annual report reflects some of the changes in research priorities which have resulted from our continuing critical review and re-appraisal of our research directions and of our concept of the role of the ARC. In the clinical biology area, new emphasis is being given to the study of individual differences in psychological and physiological responsivity to drugs, including drug-induced subjective changes and vulnerability to dependence and relapse. Our already substantial program in the neurosciences has been further expanded and this area now represents one of the ARC's strongest and most comprehensive areas of concentration. In another new area of emphasis, our section on neuroendocrine function and immunology has been further strengthened and studies of the seroprevalence of the human acquired immunodeficiency virus (AIDS virus, HIV) in drug-abusing populations and the effects of selected drugs on the immune system have been initiated and, in some cases, completed.

Again, I would like to extend our thanks to the members of the Board of Scientific Counselors who served during the past year. They are: the Chairman, Nancy Mello, Ph.D. (McLean Hospital), Marian Fischman, Ph.D. (Johns Hopkins University Medical School), Reese Jones, M.D. (University of California at San Francisco), Dorothy Lewis, M.D. (New York University Medical School). These individuals have permitted us to draw freely from their expertise.

Finally, I am deeply appreciative of the efforts of every member of the ARC staff, of our visiting scientists and research fellows, and of the contract personnel with whom we work on a daily basis. Together, I believe we have made the ARC into a productive research enterprise that will continue to grow, contribute to knowledge in the field of drug abuse, and justify the support we are given.

Clinical Biology Branch

Jerome H. Jaffe, M.D., Acting Chief

Overview

The Clinical Biology Branch conducts research in human subjects on the abuse potential of drugs; the causes, effects, treatment and prevention of addictive processes; the effects of drugs of abuse on psychological and physiological functions; and on new agents that might prove useful in treating or preventing drug dependence. These studies may involve the investigation, development and improvement of treatment agents used for drug intoxication, detoxification, and long-term rehabilitation across a number of drugs of dependence, including opioids, cocaine, anxiolytics, nicotine and marijuana. This Branch also conducts research designed to characterize the metabolic disposition of drugs of abuse, to analyze drugs of abuse in biological fluids, and to develop model compounds for pharmacological investigations. An area of investigation receiving increasing emphasis involves studies of the biology of vulnerability. Such studies, currently aimed at understanding the biological factors that contribute to conduct disorder in adolescents and sociopathy in adults, are multidisciplinary in nature and involve neurophysiological, neuroendocrine and psychological assessments.

In addition to these areas of research, the Section on Neuroendocrinology and Immunology, within the Laboratory of Biology of Vulnerability, has assumed responsibility for coordinating clinical studies on the effects of drugs of abuse on the immune system and for the operation of the laboratories which test sera for HIV antibodies and urine specimens for drugs of abuse.

The Clinical Biology Branch consists of three laboratories: Chemistry and Drug Metabolism, Biology of Dependence, and Biology of Vulnerability; moreover, a major section within the Biology of Vulnerability Laboratory is the Section on Neuroendocrinology and Immunology.

Over the past year, the main themes of the Branch have included:

1. The role of nicotine in the nicotine withdrawal syndrome;

2. The pharmacology and psychomotor effects of smokeless tobacco products;

3. The interactions of acutely administered cocaine with other pharmacological agents, such as calcium channel blockers and dopaminergic agonists;

4. The metabolism of cocaine and its detectability in various body fluids, as well as the metabolism of opioids in relation to opioid effects on behavior;

5. The role of anxiety (as induced by agents such as yohimbine) motivating sedative use;

6. The role of aggression and impulsivity as risk factors in drug abuse and serotonergic mechanisms in aggression;

7. The effects of drugs of abuse (e.g., amyl nitrite) on the immune system in man and the abuse potential of inhaled nitrites;

8. Factors determining self-administration of opioids;

9. The effects of cholinergic antagonists and other agents on human performance, an Army project.

The interim progress reports for each laboratory present the projects and findings in greater detail. The various projects and ongoing work are presented under the section of the laboratory which played the dominant role in data acquisition or analysis.

Laboratory of Chemistry and Drug Metabolism — Edward J. Cone, Ph.D., Chief

Overview

The Laboratory of Chemistry and Drug Metabolism performs chemical, pharmacokinetic, metabolic and pharmacodynamic studies in human subjects in areas related to the chemistry of substance abuse. The Laboratory also performs basic research in the area of methodology development. New analytical methods are being developed to measure drugs of abuse in body fluids. Presently, studies are underway on the pharmacokinetics and pharmacodynamics of opiates. The overall program is designed to determine the relation between behavioral and physiological effects produced by opiates and opiate levels in body fluids. In a related study, the validity of current test methods employed to detect opiate use is being assessed by measuring opiates and/or metabolites in biological specimens. Validity assessment of urine screening assays for other classes of drugs of abuse is also underway.

Summary of Ongoing Research

Specific research projects which were actively pursued in FY '87 are briefly summarized below. Only those findings for which personnel from this Laboratory were the principal investigators are discussed.

A. **Behavioral and Urinary Excretion Studies of Marijuana Administered in "Brownies": Cone, E.J.; Collaborating Investigator: Johnson, R.E.**

The aim of this study is to determine if marijuana, administered to male human subjects in the form of baked "brownies," produces behavioral effects and appears in the urine as cannabinoid metabolites. Preliminary findings indicate that subjects experience a marijuana "high" from marijuana-laced brownies similar to that of smoking, but the onset of effects is slower and the time course is prolonged. Also, subjects tested positive by EMIT (Syva) and gas chromatography/mass spectrometry (GC/MS) methods for urinary cannabinoids after ingesting marijuana brownies.

B. **The Pharmacodynamics of Single Intravenous Bolus Doses of Cocaine in Humans: Cone, E.J.; Collaborating Investigators: Thompson, L., Sherer, M.A. and Kumor, K.M.**

The goal of this study is to determine the relationship between blood and saliva levels of cocaine and the behavioral and physiological effects induced by the presence (and disappearance) of cocaine. Another aim is to determine the possible acute effects of circulating levels of cocaine on prolactin and growth hormone. The results indicate that the pharmacokinetic profile of cocaine in plasma is similar to that reported in other studies. Moreover, the presence of cocaine in saliva was unequivocally confirmed for the first time. The relationship of cocaine saliva levels to plasma levels is currently being analyzed along with correlations with other pharmacological measures.

C. **Drug Assay Development Studies on Drugs of Abuse: Cone, E.J.**

The overall aim of this ongoing project is to develop specific sensitive and reliable assays for drugs of abuse in biological fluids. These assays serve to support pharmacokinetic and pharmacodynamic studies performed at the ARC. Following publication of the assay methodology, the methods become useful to other researchers performing studies on drugs of abuse. A specific and reliable methodology has been developed for the measurement of tetrahydrocannabinol (THC) in plasma by high pressure liquid chromatography with electrochemical detection. This methodology is a significant advance in marijuana assay technology since it is more specific than current radioimmunoassay techniques and much less involved than analysis by GC/MS.

D. **Studies on the Validity of Drug Testing Methodology: Cone, E.J.; Collaborating Investigators: Mell, L., and Irving, J., Navy Screening Laboratory, Norfolk, VA.**

The goal of this study is to compare test results of commercial screening assays for drugs and their metabolites in urine with test results obtained by GC/MS. Complete validity assessment profiles on assays for cocaine metabolites and opiates are being developed.

E. **The Pharmacokinetics and Pharmacodynamics of Opiate Analgesics: Cone, E.J.; Collaborating Investigators: Mell, L. and Irving, J., Navy Screening Laboratory, Norfolk, VA.**

The goals of this study include the following: to evaluate the usefulness of a heroin "marker" as a means of detecting heroin in urine and saliva of subjects after heroin abuse; to determine the possible relationship between plasma levels of active drug or metabolite, saliva levels and pharmacologic effects; to examine the use of saliva as a screening medium for opiates; and to assess the validity of commercial drug assays for opiates. Samples are currently being collected for this project and frozen for later analyses.

Publications for Fiscal Year 1987

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Biology of Dependence and Abuse Potential Assessment Laboratory -- Jack E. Henningfield, Ph.D., Chief

Overview

The Biology of Dependence and Abuse Potential Assessment Laboratory is one of three laboratories of the Clinical Biology Branch. The purposes of this Laboratory are: first, to assess the biological basis of drug dependence using quantitative experimental procedures of the behavioral and pharmacological disciplines; and second, to assess the abuse liability and physical dependence potential of selected compounds. These aims are intended to serve the overall mission of the ARC in providing a better foundation for the understanding, rational treatment and prevention of drug dependence.

Most studies are collaborative and multidisciplinary in nature and involve the electrophysiology and psychometric sections of the Cognitive Laboratory, the diagnostic capabilities of the Psychopathology and Vulnerability Laboratories, the neuroendocrine and pharmacokinetic response assessment capabilities of the Chemistry Laboratory, and the expertise of scientists in the Preclinical and Neuroscience Laboratories. With such multidisciplinary efforts, it is possible to quantitate the subjective, physiologic, behavioral, electrophysiologic, cognitive, pharmacodynamic, pharmacokinetic, reinforcing, aversive, and other effects of drugs.

In the summary that follows, research is divided into that which is ongoing (I) and that in which human testing is completed but for which followup analyses are in progress (II).

I. Summary of Ongoing Research

A. Triazolam Self-Administration: Interactions with Yohimbine: Roache, J.D., Henningfield, J.E., Meisch, R.A. and Jaffe, J.H.

Subjects with histories of sedative abuse are studied on the Residential Research Unit to determine the possible effects of anxiety induction on responses to a benzodiazepine (triazolam). The experimental model of anxiety is the response to yohimbine administration. Completion of testing in 3 subjects revealed that (1) yohimbine pretreatment did produce responses characteristic of anxiety, (2) triazolam self-administration appeared to be increased by yohimbine pretreatment, (3) triazolam produced deficits on performance and memory tasks to which some tolerance developed.

B. Behavioral and Pharmacologic Factors in Nicotine Replacement for Tobacco Dependence: Henningfield, J.E., Nemeth-Coslett, R., Snyder, F.R., Herning, R.I. and Pickworth, W.B.

A series of ongoing studies are being conducted to further characterize the pharmacology of nicotine chewing gum. These studies include assessing the effects of the dose of nicotine gum on performance and mood in tobacco-deprived cigarette smokers, nondeprived smokers, and nonsmokers. Other studies have assessed factors that determine the dose of nicotine delivered via this route, e.g., chewing rate instructions. Results from currently completed studies have practical implications for more efficacious use of the gum for treatment of tobacco dependence as well as for understanding the behavioral pharmacology of nicotine delivered via this route of administration.

C. Opioid Self-Administration: Humans Compared to Animals: Lamb, R.J., Henningfield, J.E. and Goldberg, S.R.

Subjects with histories of opioid abuse are given the opportunity to receive an intramuscular injection of morphine on the Clinical Research Unit to assess the effects of the schedule of reinforcement and drug paired stimuli on the strength and persistence of the behavior. In the 7 initial subjects tested, rates and patterns of responding were similar to those obtained when animals have been tested under analogous conditions, confirming the power of the schedule of reinforcement as well as the cross species generality of the effect. Interestingly, it appears that drug-seeking behavior may persist at dose levels which appear to be subthreshold for discrimination by conventional self-report measures.

D. Abuse Liability of Smokeless Tobacco Products: Henningfield, J.E., Radzius, A., Nemeth-Coslett, R. D., and Cone, E.J.

Two smokeless nicotine delivery systems are being evaluated using standardized procedures to assess the pharmacodynamic variables relevant to their potential liability for abuse, as well as the degree to which effects are similar to those known to be produced by cigarette smoking. One of the systems was a commercially available smokeless tobacco product (pouches of snuff) which is held in the mouth to provide buccal nicotine absorption; the other was a smokeless cigarette through which air is sucked to inhale vaporized nicotine. Both products produced orderly dose-related effects which were generally similar to cigarette smoke-delivered nicotine. A third smokeless nicotine delivery system, which is a pleasantly flavored nicotine delivering chewing gum, is currently under review for possible clinical testing.

E. Effects of Commonly Used Drugs (i.e., Alcohol, Antihistamines) on Behavioral Performance in Normal Subjects (Army Contract Related Study): Roache, J.D. and Henningfield, J.E.

Non-residential subjects are being tested in a study which is of basic interest to clinical pharmacology as well as to partially fulfill contractual obligations to the Army. The study involves the use of performance assessment and other behavioral measures to examine the effects of prescription and nonprescription drugs in normal volunteer subjects in the nonresidential paradigm. An additional purpose of these studies is to develop standardized behavioral performance assessment batteries.

F. Effects of Drugs on Cigarette Smoking and Response to Nicotine: Nemeth-Coslett, R.D., Henningfield, J.R., and Griffiths, R.R.

In an ongoing series of studies, a variety of experimental preparations are used to assess the direct effects of drugs on the rate of cigarette smoking as well as on self-reported responses to smoking (e.g., satisfaction obtained by smoking). Recently completed studies include the effects of marijuana, naloxone, nicotine gum and mecamylamine. Currently being collected and evaluated are data from the Residential Research Unit which have been (and are being) obtained as an adjunct to all clinical studies. These data include rate and pattern of cigarette smoking; they are collected from all subjects using an automated cigarette dispensing and recording system.

G. Cholinergic Agonists and Antagonists (Army Contract Related): Roache, J.D., Henningfield, J.E., Herning, R.I.

Human volunteers without histories of drug abuse, except for cigarette smoking, are tested to assess the possible adverse performance effects of a cholinergic agonist and antagonist, given singly and in combination. The Army Performance Assessment Battery (PAB), including components of the Triservices PAB, are used to evaluate behavioral performance. Data collection from human subjects is expected to be completed in early FY 88.

H. Archival Database Project: Haertzen, C.A., Chairman, Database Committee

The main purpose of the Database Committee is to combine data from diverse studies and perform analysis of the combined data, building on the extensive screening/testing program initiated by Dr. Jaffe at both the recruitment and admission levels. Database activity has been focused on assembling files of scores collected at the two time periods and linking these. This effort has permitted comparisons between tests collected at the two time periods and made it possible to relate scores on the various tasks.

II. Summary of Projects in Which Human Testing is Completed

A. Comparative Studies on Intravenous Drug Self-Administration by Monkeys and Human Volunteers: Nicotine and Cocaine. Henningfield, J.E., Goldberg, S.R., Nemeth-Coslett, R.D., Lamb, R.J., Katz, J.L. and Schindler, C.

Volunteers were given access to intravenous nicotine and cocaine in a paradigm similar to that employed to study the reinforcing effects of drugs in animals. Such studies permit comparison of findings obtained with animals and humans and thereby offer the opportunity to cross-validate human and animal models of drug abuse. In addition, the studies can yield data not possible from studies conducted with either species alone. For instance, the effects of drug-associated stimuli on drug self-administration as well as subjective reports can be made with humans; studies in animals then permit evaluation of a much more extensive range of test conditions.

In brief, the studies conducted showed that there was a considerable degree of cross-species generality in the functional effects of variables such as dose and schedule of reinforcement. In addition, an intensive study of the effects of cocaine-paired stimuli showed that they could be important in the maintenance of drug seeking as well as in relapse. The data need only to undergo final analyses before publication.

B. Acquisition of Dependence to Cigarettes and Smokeless Tobacco: Henningfield, J.E., Nemeth-Coslett, R.D., Radzius, A., Snyder, F.R., Haertzen, C.A. and Fagerstrom, K.O.

A survey was conducted in collaboration with The Johns Hopkins University School of Medicine to retrospectively assess patterns of use of cigarettes and smokeless tobacco products. The questionnaire included a scale used to evaluate level of dependence (Fagerstrom Tolerance Questionnaire). Preliminary analyses reveal that acquisition of tobacco use is marked by a gradual increase in use over many (8+) years in most tobacco users. Approximately 5% of cigarette smokers remain "chippers" (less than 6 cigarettes per day) for more than two years. There were no clear correlates of dependence development during early exposure to tobacco. However, smoking rates at 6 months were related to smoking rates and levels of dependence 8 years or more later. These data need only to undergo final analyses before publication.

C. Factors Influencing Behavioral and Physiological Response to Opioids: Henningfield, J.E., Cone, E.J., Higgins, S.T., Preston, K.L. and Jaffe, J.H.

Postaddicts and non-opioid users have been reported to respond differentially to opioids. This project was designed to experimentally examine such population differences in response to mu

and kappa opioids on subjective, behavioral, physiological and neuroendocrine parameters using post-addicts and opiate-naive normal residential volunteers. In the initial study (completed), the effects of single doses of naloxone, following either placebo or morphine pretreatment, were studied in subjects with histories of opioid dependence. Laboratory testing is complete on the first phase of the study. Initial results suggest that a single dose of morphine produces sufficient neuroadaptation such that a mild morphine withdrawal-like effect was observed when the opioid antagonist, naloxone, was subsequently administered. These data need only to undergo final analyses before publication.

D. **Physiologic Dependence to Tobacco: Cigarette Withdrawal and Nicotine Substitution: Henningfield, J.E., Nemeth-Coslett, R.D., Snyder, F.R., Herning, R.I., Pickworth, W.B. and Cone, E.J.**

Two intensive multidisciplinary collaborative studies were conducted using variations on the "direct addiction" and "substitution" strategies for assessing withdrawal and cross tolerance. In the first study, cigarette smokers were abruptly withdrawn from tobacco for ten days, and then allowed to resume smoking. In the second study, smokers were tested in repeating cycles of 4 days smoking and 3 days abstinence; during abstinence, they were given either 0, 2, or 4 mg nicotine-containing pieces of gum to chew. A characteristic withdrawal syndrome was obtained in the first study and on 0 mg gum days in the second study. Of particular interest were certain performance and electrophysiologic data that showed little tendency to recover from the decrements and alterations associated with withdrawal over the 10 day period of observation. Nicotine gum produced a dose-related blockade of withdrawal. These data need only to undergo final analyses before publication.

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Biology of Vulnerability Laboratory -- Jerome H. Jaffe, M.D., Acting Chief

Overview

This Laboratory was established to conduct studies of individual differences in acute responses to abused drugs (i.e., reinforcing effects) and to examine the mechanisms involved in those factors known to be associated with later drug abuse problems: male gender, childhood aggression, antisocial personality, biological parents with a history of alcoholism or criminality. Because of difficulties in recruiting clinical investigators, this Laboratory also assumed the major burden of initiating clinical studies of cocaine at the ARC. For most of the period covered by this report, the scientific staff consisted of one staff scientist (Dr. K. Kumor), one staff fellow (Dr. M. Sherer) who worked on a part-time basis, and one visiting scientist (Dr. D. Lozovsky). The newly formed section on Neuroendocrinology and Immunology headed by Dr. Elizabeth Dax has taken major responsibility for studies on the effects of nitrites on immune function. The diverse activities of this group are described in a separate section.

Summary of Ongoing Research

During the past year, this Laboratory has undertaken several studies, including:

A. **Effects of Acute and Repeated Cocaine Administration on EEG and Neuroendocrine Functioning;**

   In addition, extensive analyses of previously gathered data examining the effects of four-hour infusions of cocaine have been completed.

B. **Interactions of Cocaine and Other Psychoactive Agents (i.e., Studies of the Neurotransmitter(s) Involved in Cocaine Effects Using Haloperidol, Bromocriptine, and Ca++ Channel Blockers);**

C. **Differences in Serotonergic Sensitivity among Former Drug Users with High and Low Levels of Self-Reported Aggressive Behavior (the Serotonin Project);**

D. **Pharmacological Interactions of Naloxone and Putative Sigma and Kappa Agonists;**

E. **Effects of Drugs on the Immune System in Man;**

F. **The Abuse Potential of Inhaled Nitrites;**

G. **The Prevalence of HIV Antibodies in Drug Abusers from Diverse Geographical Areas of the United States.**

The studies on cocaine infusion revealed little tolerance to cardivascular or subjective effects over a four-hour period. However, the acute euphoric

sensation (called "rush") which follows rapid i.v. injections was not prolonged by a cocaine infusion. Further, there is some evidence that paranoia may develop in as brief a period as four hours if plasma levels are maintained at high and relatively constant levels.

The study entitled "Effects of Pharmacologically Induced Changes in Serotonergic Activity on Neuroendocrine Measures in Drug Addicts With and Without Aggressiveness" examines central serotonergic systems in relation to levels of aggression and impulsivity in male populations with drug abuse histories as compared to those without such histories. A serotonergic probe, fenfluramine, is administered to inpatients to evaluate the behavioral and neuroendocrine mechanisms regulated by serotonin. Selection criteria for the study include scores on three psychodiagnostic tests which determine group assignments to "high" versus "low" aggressive groups. A five-hour glucose tolerance test, including electrophysiological and insulin measures, precedes the pharmacologic testing since serotonergic activity and glucose metabolism are known to covary. In addition, some studies have shown disrupted glucose metabolism in highly aggressive individuals.

On two alternate days, either fenfluramine or placebo is administered using a double-blind procedure. Electrophysiological (EEG, event-related potentials, and skin conductance) and neuroendocrine (prolactin) measures are obtained throughout the day along with a mood state evaluation. Clinical and behavioral tests, including Diagnostic and Statistical Manual, Third Edition (DSM-III) diagnoses, are also administered to further establish levels of aggression and substance abuse. To date, 27 subjects have been admitted to this study and data on all aforementioned measures have been obtained from these individuals.

Publications and Papers - FY 1987

Papers

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Sherer, M.A., Kumor, K.M. and Jaffe, J.H.: Effects of intravenous cocaine are partially attenuated by haloperidol. Submitted September 1987.

Kumor, K.M., Sherer, M.A. and Cascella, N.G.: Cocaine Use in Man: Subjective Effects, Physiologic Responses and Toxicity. Redda, K. and Barnett, G. (Eds.): Cocaine, Marijuana, Designer Drugs: Chemistry, Pharmacology, and Behavior. Cleveland, OH, CRC Press, 1987.

Abstracts

Kumor, K.M., Sherer, M.A., Jaffe, J.H.: Haloperidol pretreatment for intravenous cocaine. Society for Biologic Psychiatry Annual Meeting, Chicago, IL, 1987.

Kumor, K.M., Sherer, M.A. and Jaffe, J.H.: Subjective and physiological responses after two sequential doses of intravenous cocaine. American College of Neuropsychopharmacology Annual Meeting, San Juan, Puerto Rico, 1987.

Lozovsky, D.B., Sherer, M.A., Kumor, K.M.: Plasma prolactin response to cocaine after haloperidol pretreatment. Society for Neuroscience Annual Meeting, New Orleans, LA, 1987.

Sherer, M.A.: Intravenous cocaine-psychiatric effects, biological mechanisms. Acceptance for William Bennett Award for Young Investigators. Society for Biologic Psychiatry Annual Meeting, Chicago, IL, 1987.

Neuroendocrinology and Immunology Section — Elizabeth M. Dax, M.D., Ph.D., Chief

Overview

Drug abusers constitute a large proportion of those people who have been exposed to the human immunodeficiency virus (HIV) or have contracted the disease of AIDS - Acquired Immunodeficiency Syndrome. It is this group of those infected with HIV who will be largely responsible for the spread of the virus into the heterosexual community. Furthermore, drugs of abuse are known to perturb immune function and, therefore, may be important cofactors in the development of AIDS in those exposed to the HIV.

The Section of Neuroendocrinology and Immunology evolved from the "AIDS Laboratory" which was established to investigate the prevalence of the HIV in drug abusers and the effects of drugs of abuse in the immune system. The AIDS Laboratory formed part of NIDA's effort to curb AIDS in the drug-abusing community by carrying out the Laboratory component of a multi-city survey of HIV antibody prevalence in known addicts. Subsequently, the Laboratory assumed responsibility for a multidisciplinary study of the effects of inhaled nitrites on the immune system. Because of the special expertise in neuroendocrinology which Dr. Elizabeth Dax, who heads this Section, possesses, the capabilities of the Biology of Vulnerability Laboratory have been significantly enhanced. This has permitted investigations into the neuroendocrine mechanisms involved in the onset and perpetuation of drug abuse (particularly the role of neuroendocrine stress responses) as well as studies of the possible interaction between these responses and changing immune function with drugs of abuse.

In addition to its research activities, the Neuroendocrinology and Immunology Section is responsible for carrying out the tests to establish the sero-status of individuals at risk for exposure to HIV. The Laboratory is supporting the NIDA national study of sero-prevalence in drug abusers. Studies originating at ARC have been carried out and further studies examining the HIV status of high risk individuals are planned.

The Neuroendocrinology Section of the Laboratory is conducting studies in human volunteers and in animals. Investigations include studies of the role of drugs of abuse in perturbing neuroendocrine responses. Initial studies will center on the mechanisms by which cocaine disrupts dopamine-mediated secretion of hormones. Moreover, hormones with known circadian periodicities in response to drug administration are being examined using human volunteers in an attempt to establish a correlation between hormonal environment and immune function.

Collaborative studies between this Section and the Immunology Section of the Gerontology Research Center (Dr. William Adler, Chief) are investigating changes in immune function in response to nitrite inhalation. The nitrites are abused primarily by homosexual men and it is these men who are the only group of AIDS sufferers with a high prevalence of Kaposi's sarcoma. Thus, it is suspected that nitrites are responsible for a disturbance in immune

function that facilitates the development of this disease. Immune function in ARC volunteers is being assessed in response to the administration of nitrites (amyl and iso-butyl) and will be measured following the administration of marijuana with and without coincident nitrite administration, since these drugs are frequently abused in combination.

The goals of this Section are:

a) to study the relationship between HIV status and clinical status of high risk subjects in relation to their drug habits.

b) to investigate the mechanisms of disturbance of neuroendocrine secretion caused by drugs of abuse.

c) to investigate the possible interactions between the disturbed mechanisms of neurosecretion and changes in immune function, and perhaps the perpetuation of a drug habit. Further, the hypothesis that drugs of abuse may be co-factors in the development of AIDS in HIV infected people will be tested.

d) to provide a service laboratory to the ARC for the measurement of hormones and drugs in body fluids and tissue extracts.

Summary of Ongoing Research

A. The Prevalence of HIV Antibodies in Drug Abusers

During 1986, a survey of HIV prevalence in intravenous (i.v.) drug abusers was made in plasma collected from 6 drug abuse treatment centers across the country. In general, it was found that there was a high prevalence of HIV seropositivity in the i.v. opioid abusers close to New York City and, as the distance from that center increased, the incidence of the HIV positive people decreased. Sharing of needles was as common in low seroprevalence areas as in high seroprevalence areas. The survey provides the basis for important intervention strategies that might be taken to prevent the spread of HIV in the drug abusing community. The survey will be repeated in the next fiscal year under the auspices of the Clinical Research Division of NIDA's extramural program. The ARC will continue to monitor trends in the Baltimore area.

The means for detecting HIV antigen (or evidence of the virus particle itself rather than the body's response to the virus) is now available. Studies are planned to assess the time between detection of the virus and detection of antibodies in the plasma of addicts. Similarly, in the Lexington followup study where antibodies to HIV have been detected in banked plasma of Lexington inmates from 1971-1972, the presence of virus, itself, will be investigated.

B. Drugs and Changes in Immune Function

Drugs of addiction are known to disturb immune function. The inhalable nitrites have received particular attention with respect to the possibility of their being etiological agents in the development of Kaposi's sarcoma in male homosexuals with AIDS. There are several possible reasons for this apparent linkage including: 1) the nitrites are carcinogenic agents; 2) they may be surrogate markers for the particular life style which may confer risk; or, 3) there may be changes in immune function that facilitate the development of the sarcoma. To investigate these possibilities, a study was conducted in which amylnitrite was administered to volunteers and their immune function was monitored. These subjects had altered immune function as exhibited by decreased white cell counts, reduced natural killer cell activity and changes in T cell numbers. A second study in which the nitrite was administered over 3 weeks (rather than over one week as in the initial study) has been carried out but the data are not yet analyzed.

Since the nitrites are often abused in combination with marijuana and alcohol, the effects of marijuana on immune function will be studied. In a subsequent study, the combined effects of marijuana and nitrites will be assessed. These findings may help decipher why Kaposi's sarcoma occurs almost exclusively in the homosexual group of AIDS patients. These studies may also have some relevance regarding possible explanations for why those infected with HIV develop AIDS and why those AIDS patients who are drug abusers have a more rapid downhill course with greater morbidity than nondrug abusers.

C. The Effect of Cocaine on Hormone Secretion from the Anterior Pituitary

Tolerance to the physiological effects of cocaine may occur after as little as one dose of cocaine. Pharmacological evidence suggests that some of this effect may be mediated by a drug induced alteration in dopaminergic neuronal function. The release of prolactin is under chronic inhibition by dopamine which is released from a discrete population of neurons contained within the medial basal hypothalamus. The release of prolactin in the male rat is an indirect assessment of dopaminergic function.

The secretion of prolactin will be assessed in rats with different susceptibilities to the addictive properties of cocaine, following the acute administration of cocaine. The direct effects of cocaine on the release of dopamine from the tuberoinfundibular neurons will be evaluated by examining release before and after cocaine in rats that are cannulated for collection of hypothalamo-hypophyseal blood. Additional experiments will be performed to determine if the effect of cocaine on prolactin release is mediated by increasing the concentrations of other prolactin releasing factors that reach the

anterior pituitary, by altering the sensitivity of receptors in the anterior pituitary cells, or by a combination of these factors.

Together, these experiments may localize the point of interference in the release of prolactin and determine the level of involvement of the dopaminergic system. The diurnal rhythms of hormones both under and not under dopaminergic control will be examined in humans known to be cocaine abusers during withdrawal from cocaine. Early results indicate that the rhythm of prolactin secretion is absent in the early phases of withdrawal, while the rhythm of cortisol secretion (not under dopaminergic control) is not. Since sleep disturbances are one of the most trying aspects of drug withdrawal, these studies may provide some insight into whether the imposition of rhythms may facilitate more comfortable withdrawal. Moreover, these studies may contribute further information regarding dopaminergic control of prolactin secretion in humans. Thus, the animal studies should complement the findings of the clinical studies.

The effects of long-term cocaine administration on the central nervous system will also be examined using an in vitro system. Pituitaries and/or hypothalami of rats chronically treated with cocaine will be perifused and the output of dopamine and neuropeptides examined concommitantly with the release of prolactin.

D. Mobilization of Pools of Peptide Hormone as a Function of Drug Environment

It has been shown that cocaine disturbs dopamine mechanisms and other drugs may similarly disorder normal hormonal secretion patterns. To complement clinical studies and the animal studies cited above, the release of anterior pituitary hormones will be studied in single dispersed anterior pituitary cells using the reverse hemolytic plaque assay. By combining this technique with autoradiographic methods and identifying cells of graded densities (in which newly formed hormone is more likely to be), identification of hormonal pools may be identified. In vitro treatment of the cells with cocaine can then be performed to determine if the use of cocaine disrupts the normal sequelae of sequestration and release of hormone.

E. Effect of MDA and MDMA on Dopamine and Serotonin in the Rat Brain

Methylenedioxymethylamphetamine (MDMA) and methylenedioxy-amphetamine (MDA) deplete serotonin and destroy serotonergic neurons when administered peripherally but not centrally. The neurotoxic effects of various doses and times of administration of these compounds was investigated in rats, guinea pigs, and mice. Progressively greater reductions in 5-hydroxytryptamine (5-HT, serotonin) and 5-hydroxyindoleacetic acid (5-HIAA) content and 5-HT

uptake sites were seen with increasing dose and time of administration in rats and guinea pigs but not in mice. The synthesized metabolites, 4-hydroxy-3-methoxyamphetamine and alpha-methyldopamine, were less potent than MDA, while alpha-methylnorepinephrine, a metabolite of MDMA, was more potent in disturbing serotonergic neuronal function.

Publications - FY 1987

Battaglia, G., Yeh, S.Y., and DeSouza, E.B.: MDMA induced neurotoxicity: Parameters of degeneration and recovery of brain serotonin neurons. Pharmacol. Biochem. Behav., In press.

Battaglia, G., Yeh, S.Y., O'Hearn, E., Molliver, M.E., Kuhar, M.J., and DeSouza, E.B.: 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxyamphetamine (MDA) destroy serotonin terminals in rat brain: Quantification of neurodegeneration by measurement of ^{3}H-paroxetine-labeled serotonin uptake sites. J. Pharmacol. Exp. Ther., In press.

Dax, E.M., Adler, W.H., Nagel, J.E., Lange, W.R., and Jaffe, J.H.: Effects of Nitrites on the Immune System of Humans. NIDA Research Series Monograph. Washington, D.C., U.S. Government Printing Office, In press.

Lange, W.R.: Viral hepatitis and international travel. Am. Fam. Physician 36: 179-184, 1987.

Lange, W.R., Cone, E.J., and Jaffe, J.H.: The prevalence of hepatitis B and human immunodeficiency virus markers in a sample of Haitian entrants. Public Health Rep. In press.

Lange, W.R. and Dax, E.M.: Human immunodeficiency virus infection and international travel. Am. Fam. Physician. In press.

Lange, W.R., Haertzen, C.A., Hickey, J.E., Snyder, F.R., Dax, E.M., and Jaffe, J.H.: Nitrite inhalants, contemporary patterns of abuse. Am. J. Alcohol and Drug Abuse. In press.

Lange, W.R., Snyder, F.R., Lozovsky, D., Kaistha, V., Kaczaniuk, M.A., and Jaffe, J.H.: The geographic distribution of human immunodeficiency virus markers in parenteral drug abusers. Am. J. Public Health. In press.

Lange, W.R., Snyder, F.R., Lozovsky, D., Kaistha, V., Kaczaniuk, M.A., and Jaffe, J.H: HIV infection in Baltimore: Antibody seroprevalence rates among parenteral drug abusers and prostitutes. Maryland Med. J. In press.

Yeh, S.Y.: N-debenzylation of pyrilamine and tripelennamine in the rat: A new metabolic pathway. Drug. Met. Dispos. 15: 466-472, 1987.

Yeh, S.Y.: Effects of repeated cocaine administration on brain monoamines in rats. Fed. Proc. 46: 404, 1987.

Battaglia, G., Yeh, S.Y., and DeSouza, E.B.: MDMA (3,4-methylene dioxymethamphetamine): Selective neurotoxic effects and interactions with brain serotonin systems. Presented at the meeting of Committee on Problems of Drug Dependence, June, 1987.

Dax, E.M., Adler, W.H., Nagel, J.E., Dorsey, B.A., and Jaffe, J.H.: Amyl-nitrite inhalation alters immune function in normal volunteers. Proceedings of the Third International Conference on Acquired Immunodeficiency Syndrome. 1987, p. 130.

Hsu, F.-L., and Yeh, S.Y.: Quantification of urinary disposition of tripelennamine (T) and pyrilamine (P) in rats. Pharmacologist 29: 149, 1987.

Hsu, F.-L., Yeh, S.Y., and Munavalli, S.: Synthesis of hydroxytri pelennamine via O-demethylation of pyrilamine. 194th American Chemical Society Meeting, Abstract, Organic Chemistry-62, 1987.

Lange, W.R., Cone, E.J., Kaczaniuk, M.A., Snyder, F.R., and Jaffe, J.H.: Potential HIV seropositivity in 1971-72 parenteral drug abusers - a followup study. USPHS Professional Association, 1987.

Lange, W.R., Primm, B.J., Tennant, F.S., Payte, J.T., Luney, C.M., and Jaffe, J.H.: The geographic distribution of human immunodeficiency virus (HIV) antibodies in parenteral drug abusers. Proceedings of the Third International Conference on Acquired Immunodeficiency Syndrome. 1987, p. 71.

Yeh, S.Y.: Metabolism of tripelennamine in humans. Pharmacologist 29: 149, 1987.

Yeh, S.Y., Battaglia, G., O'Hearn, E., Molliver, E., Kuhar, M.J., and DeSouza, E.B.: Effects of MDA and MDMA on brain monoaminergic systems: in vivo studies. Society for Neuroscience Annual Meeting Abstract, 1986, p. 1234.

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00002-02 CDM

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Validity Studies of Commercial Drug Screening Assays

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	E.J. Cone	Chief	CDM, ARC, NIDA
Others:	D. Darwin	Chemist	ARC, NIDA
	D. Yousefnejad	Chemist	ARC, NIDA
	S. Menchen	Lab Tech	ARC, NIDA
	P. Welch	Nurse	ARC, NIDA

COOPERATING UNITS *(if any)*

Naval Screening Laboratory, Norfolk, VA (J. Mitchell and L. Mell).

LAB/BRANCH

Laboratory of Chemistry and Drug Metabolism, Clinical Biology Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.25	0.25	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Commercial assays for the detection of drugs of abuse in urine change periodically and must be re-evaluated for validity of detection. Studies are designed to test the validity of new assays on clinical specimens obtained from drug users under controlled conditions.

Healthy male volunteers with a history of chemical substance abuse participate in these studies. Informed consent is obtained and all procedures are approved by the Hospital Institutional Review Board. Presently, six commercial assays for cocaine are being tested for validity with cocaine specimens. The results are being compared to gas chromatography/mass spectrometry (GC/MS) analyses.

These studies test the validity of commercial assays on clinical samples instead of "spiked" samples and provide unique information on the time course of detection, specificity and accuracy.

Validity Studies of Commercial Drug Screening Assays - Publications

Cone, E.J. and Menchen, S.L.: Lack of validity of the KDI Quik Test™ drug screen for detection of benzoylecgonine in urine. J. Anal. Toxicol., 1988. In press.

Abstract:

Cone, E.J., Menchen, S. and Mitchell, J.: Validity testing of the TD$_x^R$ cocaine metabolite assay with human specimens obtained after intravenous cocaine administration. The International Association of Forensic Toxicologists, Danff, Canada, July 28-31, 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00003-02 CDM

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Detection of Drugs of Abuse in Human Saliva

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	E.J. Cone	Chief	CDM, ARC, NIDA
Others:	D. Darwin	Chemist	ARC, NIDA
	D. Yousefnejad	Chemist	ARC, NIDA
	S. Menchen	Lab Tech	ARC, NIDA
	P. Welch	Nurse	ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Chemistry and Drug Metabolism, Clinical Biology Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.25	0.25	1.0.

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Subsequent to drug administration, the presence of drugs of abuse was studied in saliva of human subjects to determine the feasibility of drug testing with saliva.

Healthy male subjects with a history of chemical substance abuse volunteered for the studies. Informed consent was obtained and all procedures were approved by the Hospital Institutional Review Board. Following the administration of cocaine, marijuana or opiates, saliva and blood samples were collected periodically. Behavioral and physiological measures were made concurrently with collection of biofluids. Samples were analyzed by gas chromatography or radioimmunoassay (RIA). Significant correlations of blood levels with saliva levels were found for cocaine. Investigations are continuing on marijuana and opiates.

These studies provide the scientific basis for development of new non-invasive tests for drug abuse.

Z01 DA00003-02 CDM

Detection of Drugs of Abuse in Human Saliva

Publications - FY 1987

Thompson, L.K., Yousefnejad, D., Kumor, K., Sherer, M. and Cone, E.J.: Confirmation of cocaine in human saliva after intravenous use. J. Anal. Toxicol. 11: 36-38, 1987.

Thompson, L.K. and Cone, E.J.: Determination of delta-9-tetrahydrocannabinol in human blood and saliva by high performance liquid chromatography with amperometric detection. J. Chromatogr. In press, 1988.

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA00004-02 CDM

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Acute Effects of Marijuana in Humans

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	E.J. Cone	Chief	CDM, ARC, NIDA
Others:	S. Menchen	Lab Tech	ARC, NIDA
	P. Welch	Nurse	ARC, NIDA

COOPERATING UNITS (if any)
Research Technology Branch, ARC, NIDA (R.E. Johnson)

LAB/BRANCH
Laboratory of Chemistry and Drug Metabolism, Clinical Biology Branch

SECTION

INSTITUTE AND LOCATION
Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.75	0.25	0.5

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The effects of marijuana were studied in human male subjects to determine the relationships of blood, saliva and urine drug levels to behavioral effects, hormone release and performance. Marijuana was administered by smoking, oral ingestion and passive inhalation of marijuana smoke.

Healthy male volunteers with a history of marijuana use participated in the study. Informed consent was obtained and all procedures were approved by the Hospital Institutional Review Board. Subjects smoked or consumed the equivalent of one or two standardized marijuana cigarettes (2.8% delta-9-tetrahydrocannabinol [THC]) or were passively exposed to the smoke of 4 or 16 marijuana cigarettes. Physiologic and behavioral measures were taken along with blood, saliva and urine. Hormone and THC measures were made on blood by radioimmunoassay. Cannabinoid metabolites were measured by high performance liquid chromatography (HPLC) and gas chromatography/mass spectrometry (GC/MS). The acute profile of marijuana was seen as resulting from rapid absorption of THC producing behavioral effects and release of cortisol. Excretion of cannabinoid metabolites was prolonged.

The significance of these studies lies in the discovery of marijuana's effects on cortisol release when actively smoked and the appearance of behavioral effects and cannabinoid metabolites in subjects who were passively exposed to marijuana smoke.

Cone, E.J., Johnson, R.E., Darwin, W.D., Yousefnejad, D., Mell, L.D., Paul, B.D. and Mitchell, J.: Passive inhalation of marijuana smoke: Urinalysis and room air levels of delta-9-tetrahydrocannabinol. J. Anal. Toxicol., 11: 89-96, 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00005-02 CDM

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Human Pharmacodynamics of Single Doses of Intravenous Cocaine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	E.J. Cone	Chief	CDM, ARC, NIDA
Others:	D. Darwin	Chemist	ARC, NIDA
	D. Yousefnejad	Chemist	ARC, NIDA

COOPERATING UNITS *(if any)*

Clinical Biology Branch, NIDA, ARC (K. Kumor and M. Sherer).

LAB/BRANCH

SECTION

Laboratory of Chemistry and Drug Metabolism, Clinical Biology Branch

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.75	0.25	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The effects of single, intravenously administered doses of cocaine were studied in male human volunteers in order to determine the relationships of blood and saliva levels of cocaine to pharmacologic effects.

The subjects were healthy males with a history of intravenous cocaine abuse. Informed consent was obtained and all procedures were approved by the Hospital Institutional Review Board. Following a pilot dose run-up study, subjects were administered single doses of cocaine (15 mg and 40 mg) and placebo in random order with crossover design. Blood, saliva, physiological and behavioral measures were taken prior to and following drug administration. Plasma and saliva levels of cocaine were measured by gas chromatography. Correlations were made between blood and saliva levels of cocaine and other measures. Cocaine levels of saliva were found to significantly correlate with blood levels and drug-induced feelings.

The significance of these findings lies in the detection and measurement of cocaine in saliva and the high correlation with other measures. These findings provide the scientific rationale for the development of a saliva screening test for cocaine and demonstrate that cocaine levels can be determined in a non-invasive manner.

Thompson, L.K., Yousefnejad, D., Kumor, K., Sherer, M. and Cone, E.J.: Confirmation of cocaine in human saliva after intravenous use. J. Anal. Toxicol. 11: 36-38, 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA00006-01 CDM

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Pharmacokinetics and Pharmacodynamics of Opiate Analgesics

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	E.J. Cone	Chief	CDM, ARC, NIDA
Others:	D. Darwin	Chemist	ARC, NIDA
	S. Menchen	Lab Tech	ARC, NIDA
	P. Welch	Nurse	ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Chemistry and Drug Metabolism, Clinical Biology Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.25	0.75

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The effects of single doses of intramuscularly administered opiates (heroin, morphine, dilaudid, codeine, oxycodone, oxymorphone) are being studied in male human volunteers in order to determine the relationship of blood and saliva levels to pharmacologic effects. Additionally, the study is being performed to determine if a metabolic marker for heroin abuse can be found in urine.

The subjects are healthy males with a history of heroin abuse. Informed consent is obtained and all procedures are approved by the Hospital Institutional Review Board. A total of three test doses (placebo and two active doses) are administered in random order. Test measures are taken made for 24 hours and biological fluids are collected for 7 days after each test. The biological fluids will be analyzed for drug and metabolites by chromatographic and immunoassay techniques.

The significance of this study lies in the potential value of saliva as a new test medium for detection of drugs of abuse and the characterization of the time course of excretion of metabolic markers for heroin abuse in urine and saliva.

PHS 6040 (Rev. 1/84) GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00004-03 BDL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Comparative Self-Administration (Monkeys and Humans): Nicotine and Cocaine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.E. Henningfield, Ph.D.	Chief	BDL, ARC, NIDA
Others:	R. Nemeth-Coslett, Ph.D.	Staff Fellow	BDL, ARC, NIDA
	R.L. Lamb, Ph.D.	Staff Fellow	BDL, ARC, NIDA

COOPERATING UNITS *(if any)*

BPL (S.R. Goldberg); BPL (J. Katz); BPL (C. Schindler); RSB (R. Lange)

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.95	0.95	0.75

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This was a collaborative project with the BPL in which the human research was conducted on the Residential Research Unit. A parallel animal-human series of self-administration studies was conducted. Self-administration (SA) studies permit an assessment of the relative contribution of environmental and pharmacologic factors to the self-administration of drugs. Parallel comparative studies in squirrel monkeys and humans in which subjects are given the opportunity to self-administer comparable doses of cocaine and nicotine under similar behavioral schedules and experimental conditions provide a means to assess the generality of biological variables influencing drug SA.

These studies also permit evaluation of the role of environmental variables and the role of conditioning in human drug taking behavior and determination of whether those roles differ from the roles of those variables in animal models of drug taking. These studies have shown that responding is maintained in human subjects in the same manner in which it is maintained in non-human experimental subjects. The stimuli that are associated with injections of cocaine develop conditioned reinforcing effects in the humans in a manner similar to the manner in which these effects develop in squirrel monkeys. Besides yielding specific data of potential theoretical and clinical interest, these studies have demonstrated that a research strategy employing drug SA in human subjects can yield all of the important information of "single-dose" studies and, also, provide information on the direct reinforcing effects of the compound which may be compared to the large database of animal drug SA studies. These data need only to undergo final analyses before publication.

Z01 DA00004-02 BDL

Comparative Studies of Drug Self-Administration in Monkeys and Human Volunteers: Nicotine and Cocaine

Publications:

Goldberg, S.R. and Henningfield, J.E.: Nicotine as a reinforcer in humans and experimental animals. Pharmacol. Biochem. Behav., 1986.

Henningfield, J.E., Nemeth-Coslett, R., Katz, J.L. and Goldberg, S.R. Intravenous Cocaine Self-Administration by Human Volunteers: Second-Order Schedules of Reinforcement. In L.S. Harris (Ed.), Problems of Drug Dependence, 1986, NIDA Research Series Monograph 76, Washington, D.C., U.S. Government Printing Office, 1987, pp. 266-273.

Ritz, M.D., Lamb, R.J., Goldberg, S.R. and Kuhar, M.J.: Cocaine receptors related to drug self-administration and substance abuse. Progr. in Neuropsychopharmacol. Biol. Psychiat., 1987, In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00024-01 BDL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Opioid Self-Administration in Humans Compared to Animals

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.E. Henningfield, Ph.D.	Chief	BDL, ARC, NIDA
Others:	R.J. Lamb	Staff Fellow	BDL, ARC, NIDA
	S.R. Goldberg	Chief	BPL, ARC, NIDA
	J.L. Katz	Staff Fellow	BPL, ARC, NIDA
	C.W. Schindler	Staff Fellow	BPL. ARC, NIDA
	W.R. Lange	Medical Officer	RSB, ARC, NIDA
	R.A. Meisch	Visiting Scientist	Univ. of Minnesota

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.95	0.95	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A series of studies with animals, including squirrel monkeys, has shown that stimuli associated with drug delivery can come to function as variables that partially control drug seeking behavior and that contribute to the likelihood of resumption ("relapse") of such behavior, even in the absence of the drug. Analogous research strategies are being used to assess the generality of these findings to human subjects. In addition, these procedures provide data on the degree of correspondence between self-reported drug effects and drug seeking behavior.

The human studies have produced a number of interesting results. When the effects of varying the dose of morphine available were examined on self-administration, physiological effects, and self-reported effects, it was found that low doses of morphine (3.75 mg) reliably maintained rates of responding above placebo and constricted pupil diameter, but did not reliably alter the self-reports of the subjects, indicating a dissociation of the subjective effects of morphine and morphine's reinforcing properties. Another manipulation evaluated the role of a stimulus paired with drug administration on the maintenance of responding. Initial results also suggest that under the conditions of this study such stimuli were less functionally important than in an analogous study with animals and in a somewhat similar study of cocaine self-administration by humans. The basis for these differences is currently under investigation.

Brady, J.V., Griffiths, R.R., Heinz, R.D., Ator, N.A., Lukas, S.E. and Lamb, R.J. Assessing Drugs for Abuse Liability and Dependence in Laboratory Primates. In Bozarth, M.A. (Ed.): Methods of Assessing the Reinforcing Properties of Abused Drugs. New York, Springer-Verlag, In press, 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00005-03 BDL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Abuse Liability of Smokeless Tobacco Products

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J.E. Henningfield	Chief	BDL, ARC, NIDA
Others:	R. Nemeth-Coslett	Staff Fellow	BDL, ARC, NIDA
	A. Radzius	Research Assistant	BDL, ARC, NIDA

COOPERATING UNITS *(if any)*

Chemistry and Drug Metabolism Lab (E.J. Cone)
Division of Clinical Pharmacology and Experimental Therapeutics
University of California, San Francisco (N.L. Benowitz)

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.85	0.35	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In two studies, tobacco users were given a variety of doses of smokeless tobacco in either the form of a commercially available smokeless tobacco product (pouches of snuff) which is held in the mouth, or a smokeless cigarette through which air is sucked to inhale vaporized nicotine. Standardized methods of abuse liability assessment were used.

The smokeless tobacco study consisted of two phases: the first, to evaluate the effects of dose; and the second, to investigate the possibility that rate of expectoration would alter nicotine extraction and effects. Dose-related changes in magnitude and duration of action were found on measures such as reduction in urge to smoke and strength of effects. Plasma nicotine levels were closely related to dose administered, confirming the reliability of this system of nicotine delivery.

In the smokeless cigarette study, the effects of dose were similarly studied as in smokeless tobacco. Interestingly, despite finding similar dose-related effects as described above, blood nicotine levels were negligible, suggesting the possibility that this route of administration produces effects mediated by nicotine's peripheral stimulus properties which resemble those of smoking cigarettes.

A third nicotine delivery system, a pleasantly flavored nicotine chewing gum, is currently under review for possible clinical testing for abuse liability and to compare its kinetics to that of other forms of nicotine delivery.

Z01 DA00005-03 BDL

Abuse Liability of Smokeless Tobacco Products

Publications:

Henningfield, J.E.: How Tobacco Produces Drug Dependence. In J.K. Ockene (Ed.): The Proceedings of the World Congress on the Pharmacologic Treatment of Tobacco Dependence. Cambridge, MA, Institute for the Study of Smoking Behavior and Policy, 1986, pp. 19-31.

Cullen, J.W., Blot, W., Henningfield, J.E., Boyd, G., Mecklenberg, R. and Massey, M.M.: Health consequences of using smokeless tobacco: Summary of the advisory committee's report to the surgeon general. Public Health Rep. 101: 355-373, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00025-03 BDL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Acquisition of Dependence to Cigarettes and Smokeless Tobacco

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.E. Henningfield	Chief	BDL, ARC, NIDA
Others:	R. Nemeth-Coslett	Staff Fellow	BDL, ARC, NIDA
	J. Grabowski		
	C. Haertzen	Research Psychologist	BDL, ARC, NIDA
	F. Snyder	Statistician	BVL, ARC, NIDA
	A. Radzius	Research Assistant	BDL, ARC, NIDA
	K.O. Fagerstrom & A.B. Leo		Sweden

COOPERATING UNITS *(if any)*

Chemistry and Drug Metabolism Laboratory (E.J. Cone)
Research Support Branch (W.R. Lange)

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.85	0.35	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Questionnaires were given to populations of experienced cigarette and/or smokeless tobacco (SLT) users (785 responses), and to a population which included persons who had never used tobacco (496 responses). The purpose of the questionnaires was to determine changes in the amount of tobacco products consumed as a function of time and to assess the level of nicotine dependence as measured by the Fagerstrom Tolerance Questionnaire (FTQ). Findings that have emerged from initial analysis of the first population include the following: (1) SLT use begins about one year earlier than cigarette use (15.5 vs 16.3). (2) Males began smoking about one year earlier than females. (3) Tobacco consumption increased over time ("dose graduation"). (4) The dose escalation was negatively accelerated with no difference between sexes. (5) Age of starting smoking is negatively correlated with age of quitting and also with predicted FTQ scores after the same number of years of smoking. (6) Four of eight questions on the FTQ scale are correlated with total FTQ score. Analyses in progress are: (1) Analysis of brands smoked. (2) Prediction of dependence based on the amount of tobacco product consumed at some early point in history. (3) Analysis of data from the 496 response population. These data need only to undergo final analyses before publication.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00006-02 BDL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Triazolam Self-Administration: Effects of Yohimbine Pretreatment

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.E. Henningfield	Chief	BDL, ARC, NIDA
Others:	J.D. Roache	Staff Fellow	BDL, ARC, NIDA
	A. Meisch	Visiting Scientist	BDL, ARC, NIDA

COOPERATING UNITS *(if any)*

Biology of Vulnerability (J.H. Jaffe)
Research Support Branch (W.R. Lange)

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.3	1.1	1.2

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this study is to examine the effects of yohimbine pretreatment on the self-administration of triazolam in subjects with histories of sedative abuse. Two issues of relevance to the behavioral pharmacology of drug abuse are being addressed. A first objective involves the development of procedures to measure sedative/anxiolytic drug self-administration in humans. A second objective is to examine the effects of yohimbine pretreatment on triazolam self-administration. It is of basic theoretical, as well as clinical, interest to define methods to detect the effects of one drug on the self-administration of another drug. In addition, yohimbine has been shown to produce neuroendocrine changes and subjective mood states in humans which resemble anxiety. Thus, this study could provide important information related to hypotheses of drug abuse which involve psychiatric vulnerability factors (e.g., "self-medication" or "need" hypotheses).

Subjects are given the opportunity to take triazolam or a placebo following pretreatment with yohimbine or placebo. Possible changes in vulnerability to abuse, measured by triazolam self-administration and self-reported effects, are obtained. In addition, measures of performance and mood are also used to quantitate the effects of yohimbine and triazolam singly and in combination. Completion of testing on three subjects revealed that (1) yohimbine pretreatment did produce responses characteristic of anxiety, (2) triazolam self-administration appeared to be increased by yohimbine pretreatment, (3) triazolam produced deficits on performance and memory tasks which appeared to show tolerance.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00007-03 BDL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effects of Commonly Used Drugs on Behavioral Performance in Normal Subjects

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.E. Henningfield	Chief	BDL, ARC, NIDA
Others:	J.D. Roache	Staff Fellow	BDL, ARC, NIDA
	R.A. Meisch	Visiting Scientist	BDL, ARC, NIDA

COOPERATING UNITS *(if any)*

Research Support Branch (W.R. Lange)

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.35	1.35	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The possible adverse effects of an antihistamine and alcohol on performance are being evaluated in non-residential subjects without histories of drug abuse, other than cigarette smoking. The study involves the use of strategies recommended by the Joint Triservices Working Group (Army contract) to assess behavioral performance. Measures included the standard Army Performance Assessment Battery (PAB), prototypic portions of the Unified Triservices Battery (UTC PAB), critical flicker fusion, mood, cardiovascular and other basic physiologic variables.

Preliminary analyses of data suggest that alcohol and chlorpheneramine produced dose-related effects on several self-report measures and mixed effects on performance across measures. These initial results suggest that the PAB is less sensitive, when compared to the Digit Symbol Substitution Task, in the level of disruption by alcohol or chlorpheramine.

A new protocol is being developed for FY 88 in accordance with the Army contract. The main objective of this protocol will be to compare a new antihistamine which seems to have only weak CNS effects (terphenadine) to more commonly used antihistamines to determine if it offers significant reduction of performance impairment at therapeutic dose levels. This protocol will also incorporate the upgraded version of the UTC PAB to assess its sensitivity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00008-03 BDL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Behavioral Performance and Physiologic Effects of Drugs: Atropine and Diazepam

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.E. Henningfield	Chief	BDL, ARC, NIDA
Others:	R.J. Lamb	Staff Fellow	BDL, ARC, NIDA
	S.T. Higgins	Staff Fellow	BDL, ARC, NIDA

COOPERATING UNITS *(if any)*

Cognitive Studies and Human Performance Lab (R.I. Herning; W.B. Pickworth; F. Snyder); Research Support Branch (W.R. Lange)

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.1	1.1	2.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies were conducted to assess the effects of drugs which may be given under conditions in which a person is expected to maintain effective performance on various tasks. An additional aspect of this research was to identify possible electrophysiological correlates including changes in passive electroencephalogram (EEG) as well as evoked cortical potentials. Therefore, these studies are conducted in collaboration with the Cognitive and Human Performance Laboratory in which EEG and evoked potential data are collected. Atropine and diazepam were tested and found to produce orderly and dose-related effects on a variety of measures of subjective response as well as on performance on the computerized Performance Assessment Battery (PAB). This basic methodology has also been used in studies of other drugs under assessment at the Addiction Research Center including opioids, cocaine, and nicotine.

These studies have been completed and data analyses are underway. Preliminary analyses of the results from the study on diazepam indicate that most measures were affected in an orderly time and dose-related manner. However, most measures were surprisingly insensitive and significant effects were often not seen until the administration of the highest dose of diazepam (40 mg). The measures developed by the Army did not appear to be more sensitive than traditional measures (e.g., DSST). These data need only to undergo final analyses before publication.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00009-04 BDL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effects of Drugs on Cigarette Smoking and Response to Nicotine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.E. Henningfield	Chief	BDL, ARC, NIDA
Others:	R.D. Nemeth-Coslett	Staff Fellow	BDL, ARC, NIDA

COOPERATING UNITS *(if any)*

The Johns Hopkins University School of Medicine (R.R. Griffiths)

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	.2 (includes JHU support)

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Some of these studies were conducted in the physical facilities of the Behavioral Pharmacology Research Unit at the Johns Hopkins University. For instance, multiple measures of cigarette smoking, subjective effects and physiologic effects were collected during ad libitum smoking sessions in normal volunteers following administration of mecamylamine, naloxone, or marijuana. Mecamylamine had effects opposite to those of nicotine on several measures of smoking and subjective response: mecamylamine increased smoking and had some sedating effects. However, the two drugs similarly decreased the satisfaction derived from smoking. Marijuana and naloxone had weak and variable effects on smoking; these findings are not consistent with either the hypothesis that smoking is substantially mediated by endorphin release or the hypothesis that smoking is simply related to level of "positive" subjective state.

Presently, basic measures of cigarette smoking are being collected from all subjects on the clinical research unit and data analyses have begun. This "database" type of study appears to be providing the opportunity to quantitate the effects of a wide range of variables on cigarette smoking (i.e., atropine administration, cocaine withdrawal, buprenorphine administration, and passive tobacco smoke exposure).

Z01 DA00009-04 BDL

Effects of Drugs on Cigarette Smoking and Response to Nicotine

Publications

Nemeth-Coslett, R.D. and Griffiths, R.R.: Naloxone does not affect cigarette smoking. Psychopharmacology 88: 420-425, 1986.

Nemeth-Coslett, R.D., Henningfield, J.E., O'Keeffe, M.K. and Griffiths, R.R.: Effects of mecamylamine on human cigarette smoking and subjective ratings. Psychopharmacology 88: 420-425, 1986.

Nemeth-Coslett, R.D., Henningfield, J.E., O'Keeffe, M.K. and Griffiths, R.R.: Effects of marijuana on human cigarette smoking and physiologic changes and subjective responses. Pharmacol. Biochem. Behav. 25: 659-665, 1986.

Nemeth-Coslett, R., Henningfield, J.E., O'Keeffe, M.K. and Griffiths, R.R.: Nicotine gum: Dose-related effects on cigarette smoking and subjective ratings. Psychopharmacology 92: 424-430, 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00010-04 BDL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Behavioral and Pharmacologic Factors in Nicotine Replacement for Tobacco Dependence

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.E. Henningfield	Chief	BDL, ARC, NIDA
Others:	R.D. Nemeth-Coslett	Staff Fellow	BDL, ARC, NIDA

COOPERATING UNITS *(if any)*

Cognitive Studies and Human Performance Laboratory (R.I. Herning; W.B. Picworth; F. Snyder); Research Support Branch (W.R. Lange)

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.95	0.45	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Nicotine polacrilex (chewing gum) has been under investigation as a replacement for tobacco-delivered nicotine and also as a convenient drug administration modality which provides a model of general interest for drug dependence researchers. For instance, nicotine gum was employed in initial studies to evaluate the capabilities of the recently established performance and electrophysiologic assessment laboratories for assessing drug effects. The course of research using this compound has been determined by the priorities and interests of the Addiction Research Center and the Chief of the Biology of Dependence Laboratory. These studies have included the following: (1) Effects of nicotine replacement on cigarette smoking and tobacco smoke exposure; (2) Pharmacodynamic effects of nicotine compared to other routes of nicotine administration; (3) Abuse liability of nicotine gum; (4) Dose-related effects on subjective, behavioral, and physiologic variables including studies on factors which may affect the functional dose such as chewing rate and swallowing rate; (5) Effects of nicotine gum administration on learning and performance in nonsmokers. As might be expected, nonsmokers were more sensitive to nicotine administration than smokers, but their physiologic responses were qualitatively similar to those produced when nicotine is given to tobacco users. Of particular interest was the finding that, unlike smokers, nicotine administration in nonsmokers appeared to produce dose-related impairments in performance, suggesting that performance-enhancing effects of nicotine are limited to nicotine tolerant (possibly during withdrawal) individuals.

Z01 DA00010-04 BDL

Behavioral and Pharmacologic Factors in Nicotine Replacement for Tobacco Dependence

Publications

Nemeth-Coslett, R.D., Benowitz, N.L., Robinson, N. and Henningfield, J.E.: Nicotine gum: Effects of chew rate on physiologic and self-reported responses and plasma level of nicotine. Pharmacol. Biochem. Behav. In press.

Pickworth, W.B., Herning, R.I. and Henningfield, J.E.: Electroencephalographic effects of nicotine gum in humans. Pharmacol. Biochem. Behav. 25: 879-882, 1986.

Henningfield, J.R. and Jasinski, D.R.: Pharmacological Basis for Nicotine Replacement. In O.F. Pomerleau, C.S. Pomerleau, K.O. Fagerstrom, J.E. Henningfield and J.R. Highes (Eds.): Nicotine Replacement: A Critical Evaluation. New York, Alan R. Liss, In press.

Waranch, H.R., Henningfield, J.E. and Edmunds, M.: Case report: Elimination of nicotine gum use following successful replacement therapy for cigarette smoking. Submitted to the Am. J. Psychiatr.

Snyder, F.R. and Henningfield, J.E.: Effects of acute nicotine deprivation and administration: Assessment on computerized performance tasks. Submitted to Psychopharmacology.

Pickworth, W.B., Herning, R.I. and Henningfield, J.E.: Mecamylamine reduces some EEG effects of nicotine chewing gum in humans. Pharmacol. Biochem. Behav., In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00011-04 BDL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Physiologic Dependence to Tobacco: Cigarette Withdrawal and Nicotine Substitution

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.E. Henningfield	Chief	BDL, ARC, NIDA
Others:	R.D. Nemeth-Coslett	Staff Fellow	BDL, ARC, NIDA
	A. Sampson	LPN	BDL, ARC, NIDA

COOPERATING UNITS *(if any)*

Cognitive Studies and Human Performance Laboratory, RSB (W.R. Lange)

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.4	0.4	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Heavy tobacco users, otherwise without drug abuse histories, were studied on the Residential Research Unit. In the withdrawal study, subjects were assessed for changes in mood, feeling and symptomatology, performance, sleep patterns, plasma nicotine and cotinine, general cardiovascular functioning, passive EEG and evoked cortical potential, and caloric intake, during 10 days of cigarette deprivation and when smoking resumed. In the substitution phase of the study, subjects were tested during alternating cycles of 4 days smoking and 3 days abstinence. In this phase, subjects were similarly assessed as described above, but on days in which they were not permitted to smoke, they were given pieces of gum to chew 12 times per day at one hour intervals: the gum contained either 0,2 or 4 mg of nicotine. It was found that an orderly withdrawal emerged characterized by impaired performance, which did not recover within the ten days of abstinence, but which did recover when cigarette smoking resumed. Nicotine gum reversed major signs of tobacco withdrawal, confirming that the withdrawal was nicotine specific. This effect was dose-related, (e.g., 4 mg gum restored performance to baseline levels, whereas 2 mg gum only partially restored performance). Placebo gum use was accompanied by withdrawal. Together, these results confirm that nicotine replacement can be a viable mode of alleviation of the tobacco withdrawal syndrome, but is of little benefit in reducing desire to smoke (which appears to be pharmacologically related to abstinence but appears readily elicited by environmental stimuli). These data need only to undergo final analyses before publication.

Publication: Henningfield, J.E. and Snyder, F.: Effects of acute nicotine deprivation and administration: Assessment on computerized performance tasks. Manuscript submitted to Psychopharmacology, 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00012-04 BDL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Factors Influencing Behavioral and Physiologic Response to Opioids (Mu Project)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: J.E. Henningfield	Chief	BDL, ARC, NIDA
Others: S.T. Higgins	Staff Fellow	BDL, ARC, NIDA

COOPERATING UNITS *(if any)*

The Johns Hopkins University (K.L. Preston); Biology of Vulnerability (J.H. Jaffe); Chemistry and Drug Metabolism (E.J. Cone)

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.4	0.4	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Following from the observations that post-addicts and non-opioid users are differentially sensitive to opioids, and perhaps even respond qualitatively differently, as well as from the possibility that such differences either predispose certain persons to opioid abuse and/or contribute to relapse, this study was conducted to experimentally examine such population differences in response to mu and kappa opioids. Prominent measures included discrimination thresholds of behavioral effects, physiologic responses, and neuroendocrine response. Post-addict and opioid-naive subjects were intended to be separately tested for comparison. Testing is completed on the initial phase involving post-addict volunteers. Changes in priorities, however, resulted in the termination of the protocol before opioid-naive subjects were tested. Initial results suggest that a single dose of morphine is sufficient to measure a mild withdrawal-like effect when the opioid antagonist, naloxone is subsequently administered. These data need only to undergo final analyses before publication.

Publication: Higgins, S.T., Preston, K.L., Cone, E.J., Henningfield, J.E. and Jaffe, J.H.: Behavioral, Physiological, and Hormonal Effects of a Aaloxone Challenge following Acute Morphine Treatment in Humans. In: L.S. Harris (Ed.): Problems of Drug Dependence, 1987. NIDA Research Series Monograph. Washington, D.C., U.S. Government Printing Office, In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00013-03 BDL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Archival Database

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	C. Haertzen	Research Psychologist	BDL, ARC, NIDA
Others:	J.E. Henningfield	Chief	BDL, ARC, NIDA
	A. Haynes	Research Technician	BDL, ARC, NIDA

COOPERATING UNITS *(if any)*

Biology of Vulnerability (J.H. Jaffe); The Johns Hopkins University; The Addiction Research Foundation; Cognitive Studies and Human Performance Laboratory (F. Snyder)

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.55	1.05	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Current data obtained by the recruitment staff (Addiction Research Severity Index, SCL-90, Shipley IQ, Early Childhood Aggression) and admission test data (Diagnostic Interview Schedule, Buss-Durkee Hostility, Minnesota Multiphasic Personality Inventory [MMPI], Alcohol Related Behavior Questionnaire, and EEG) have been combined into a single database. Results of these analyses will be reported by the Psychology of Vulnerability Laboratory.

A database comprised of 97 opiate addicts given the Addiction Research Severity Index under no-drug and morphine (20 mg, i.m.) conditions and the MMPI under a non-drug condition was assembled. Interest in this database was focused on the question of whether a high level of hostility constituted a risk factor for feeling greater morphine effects. Hostility was positively related to four morphine related scales. Furthermore, those high on hostility had twice the change in elevation on a simulated opiate scale as those who were low. A completed database on drug use was accessed for obtaining the prevalence of nitrite use. Nitrite use was more common in a sample of alcoholics in treatment (22%) than in drug abusers. A number of papers were derived in part from the Admission Database which is comprised of many tests. Results of these analyses will be reported by the Psychology of Vulnerability staff.

Publication: Haertzen, C.A. and Hickey, J.D. Addiction Research Center Inventory (ARCI): Measurement of euphoria and other drug effects. In: Bozarth, M.A. (Ed.): Methods of Assessing the Reinforcing Properties of Abused-Drugs. New York, Springer Verlag, In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00014-01 BDL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cholinergic Agonists and Antagonists

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.D. Roache	Staff Fellow	BDL, ARC, NIDA
Others:	J.E. Henningfield	Chief	BDL, ARC, NIDA

COOPERATING UNITS *(if any)*

Cognitive Studies and Human Performance Laboratory (R. Herning)

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.55	1.05	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Human volunteers without histories of drug abuse, except for cigarette smoking, are tested to assess the possible adverse performance effects of a cholinergic agonist and antagonist, given singly and in combination. A dose escalation procedure is conducted with the cholinergic agonist (physostigmine) to determine a dose which can be safely given but at which reliable behavioral and physiologic effects are observed. The anticholinergic (methscopolamine) is then given to assess the degree to which non-central blockade reduces physiologic effects and or performance impairment. The Army Performance Assessment Battery (PAB), including components of the Triservices PAB, is used to evaluate behavioral performance. Data collection from human subjects is expected to be completed in early fiscal year 88.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00001-02 BVL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Dopaminergic Mechanisms and Cocaine Effects

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.H. Jaffe	Acting Chief	BVL, ARC, NIDA
Others:	K. Kumor	Clinical Pharmacologist	BVL, ARC, NIDA
	M. Sherer	Staff Fellow	BVL, ARC, NIDA
	N. Cascella	Staff Fellow	BVL, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Biology of Vulnerability Laboratory, Clinical Biology Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.9	0.9	2.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

1. Cardiovascular mechanisms in the human abuse of cocaine: Assessment was made of the effects of haloperidol, a dopamine blocking agent, on the cardiovascular effects of cocaine, in order to evaluate the relevance of dopaminergic neurotransmission.

As has been demonstrated by earlier work in this laboratory, intravenous doses of cocaine were followed within minutes by elevations in systolic and diastolic blood pressure and heart rate. The dose administered in this study, 40 mg i.v., is perceived by patients as similar to a moderate street dose of the drug; this is consistent with perceptions of experienced cocaine users. In this population, 8 mg of haloperidol was not associated with significant declines in blood pressure. However, when administered 20 minutes before cocaine, haloperidol blocked the cocaine induced rise in both systolic and diastolic blood pressures, although there was little effect on cocaine related rise in heart rate.

The findings are consistent with suggestions that the pressor effects of cocaine in man are mediated via catecholaminergic mechanisms; the role of alpha adrenergic neurotransmission appears central to this process. The significance of this finding lies in the ability to predict clinically relevant interventions for some of the physiologic toxicity of cocaine.

2. Dopaminergic mechanisms and the subjective effects of cocaine: Previous work in this laboratory has confirmed several clusters of subjective and psychiatric effects of intravenous cocaine. Clinical case reports have suggested that, although haloperidol is a potent antipsychotic and may block the development of paranoia in human cocaine abusers, it has little effect on the subjective effects of the drug. Using a battery of self-ratings developed by this group, the ability of haloperidol to block these subjective effects was assessed. Cocaine was administered to 5 addict volunteers using a dose (40 mg i.v.) which produced subjective effects that resembled their street doses of the drug. Twenty minutes prior to cocaine administration, patients received a dose of 8 mg haloperidol. The study also used control conditions of haloperidol pretreatment followed by placebo administration i.v., and placebo pretreatment followed by 40 mg cocaine. The results indicate that with a 20 minute pretreatment interval, haloperidol pretreatment had no effect on the perception of drug "rush". There was some effect of haloperidol on perception of drug "high" (measured by self analogue self-ratings and by subscales of the Addiction Research Center Inventory (ARCI). Overall, the cocaine experience was rated as very pleasurable by the addict, despite haloperidol pretreatment.

This work suggests:

a. Differences in neurochemical modulation of various subjective effects of cocaine.

b. That although haloperidol is useful in the treatment of cocaine induced psychosis, it does not appear to be useful, at the interval tested in clinically relevant doses, in the prevention of cocaine induced euphoria. Further studies with a longer interval between pretreatment and challenge may be in order.

3. Neurochemical aspects of cocaine infusions: Cocaine has long been assumed to block the synaptic reuptake of catecholamines, including norepinephrine (NE) and dopamine (DA). Despite an abundance of experimental work in animals, there have been few studies in humans assessing synaptic transmission of catecholamines following i.v. cocaine administration. Thus, these studies evaluated catecholamine transmission by measuring plasma concentrations of norepinephrine and its metabolite, 3-methoxy-4-hydroxy-mandellic acid (MHPG), and the dopaminergic metabolite, homovanillic acid. In addition, peripheral sympathetic activity was examined by monitoring cardiovascular measures. Cocaine was administered as a continuous intravenous infusion over a period of four hours.

Despite a robust rise in systolic and diastolic blood pressure following cocaine administration, no accompanying rise in plasma NE was seen. Rather, a small but significant decrease in plasma NE was seen in comparison with baseline (preinfusion) controls. This decrease was paralleled by a decrease in plasma MHPG. Under certain circumstances desipramine, a prototypic uptake blocker, is associated with declines in plasma norepinephrine; this likely reflects preferential activity at the alpha-2 presynaptic receptor site. The dissociation between plasma levels of amines and cardiovascular response suggests differences in the mechanisms of amines which underlie these effects, possibly reflecting differences between central and peripheral compartments.

4. Bromocriptine pretreatment for cocaine abuse: Bromocriptine has been suggested as a potential treatment for cocaine addicts. This is likely related to its action at the dopaminergic receptor. There is currently evidence for both hyper- and hypodopaminergic states as a consequence of cocaine abuse. In a group of experienced cocaine users, the ability of pretreatment with bromocriptine to block subjective effects of acutely administered intravenous cocaine is being examined. Further, the possible effects of bromocriptine on the craving addict's experience shortly after cocaine administration are being assessed. Preliminary evidence suggests that while chronic use of bromocriptine may help reduce baseline drug craving, the effects of single doses of bromocriptine pretreatment on the subjective effects of cocaine are limited.

5. Description and assessment of "acute" craving after cocaine injection and the effects of the interaction with bromocriptine: If the pattern of cocaine use by addicts is observed, it may be possible that, after each injection, subjects will report the presence of a strong desire to repeat the pleasurable experience of the first "high" or "rush" induced by cocaine. Thus, the goal of this project is to describe the phenomenology of this craving, its time course and the effects of bromocriptine, a dopaminergic agonist, on this kind of craving. To date, nine male volunteers have participated in the study. All were chronic drug users. A double blind design during which the subjects received bromocriptine or placebo at 8 a.m. and cocaine or placebo at 10 a.m. was used. The assessment of the craving with a "Checklist for drug related feelings" was made five times during the study day. The data indicate that the cocaine condition increased the craving and the bromocriptine did have an effect in reducing this kind of craving.

Publications

Sherer, M.A., Kumor, K.M. and Jaffe, J.H.: Effects of intravenous cocaine are partially attenuated by haloperidol. Submitted, September 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00002-02 BVL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Multidimensional Scaling of Subjectively Induced Drug Effects

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	K. Kumor	Clinical Pharmacologist	BVL, ARC, NIDA
Others:	C. Haertzen	Senior Investigator	BDL, ARC, NIDA
	C. Clark	Senior Investigator	Columbia Neuropsychiatric Inst.
	J. Janal	Investigator	Columbia Neuropsychiatric Inst.

COOPERATING UNITS *(if any)*

Columbia Neuropsychiatric Institute, NY

LAB/BRANCH

Biology of Vulnerability Laboratory, Clinical Biology Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.3	0.3	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

There are multiple brain receptors which bind opiate drugs. The psychopharmacologic and physiologic effects of agonism at these different receptors is not precisely known in man. This study will attempt to analyze subjective report data using multidimensional scaling techniques. The data are subjectively judged similarities between drugs. Volunteers were given a training series of single injections of unknown opioid drugs (including placebo and naloxone). Then in a second test set of injections they were asked how similar the test drug of that day was to each of the training doses. The data obtained this way can then be analyzed with multidimensional mathematical fitting using sophisticated computer programs. The data may result in maps of the psychopharmacologic space in which drugs are arranged by their similarity to each other. This kind of map may be useful because the number of dimensions and the coordinates of a drug in dimensional space indicate the number of different kinds of receptors at which the drugs mapped are active as well as characterize the receptor type.

The results of this study are very encouraging. The maps generated with this computer technique are conceptually similar to the more crude technique we had employed earlier. This more rigorous analysis confirms our impression that this kind of work could be useful in predicting the receptor types involved in pharmacologic responses to opiate drugs in man. A paper is being prepared to report this work.

Publications: None

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00003-02 BVL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Pharmacologic and Behavioral Effects of Calcium Channel Blockers on Cocaine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.H. Jaffe	Acting Chief	BVL, ARC, NIDA
Others:	R. Lange	Medical Officer	AID, ARC, NIDA
	K. Kumor	Clinical Pharmacologist	BVL, ARC, NIDA
	R. Herning	Senior Investigator	CHP, ARC, NIDA
	W. Pickworth	Senior Investigator	CHP, ARC, NIDA
	C. Muntaner,	Fellow	PVL, ARC, NIDA

COOPERATING UNITS *(if any)*

Cognitive Studies and Human Performance Lab, Psychopathology & Cognitive Studies

LAB/BRANCH

Biology of Vulnerability Laboratory, Clinical Biology Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Calcium channel blockers have been reported to reduce toxicity in a rat model of fatal cocaine poisoning. These drugs have also been studied in a monkey model at the Addiction Research Center. In these studies on calcium channel blocker, nimodipine, was found to block some of the cardiovascular responses (increases in channels are important in a number of neurological processes and have been reported to have an uneven distribution in the brain. Therefore, the the cardiovascular and subjective responses to pretreatment with a Ca+ channel blocker drug, nifedipine, prior to cocaine challenge have been assessed. Nifedipine 10 mg is given 20 minuted before a challenge of cocaine 40 mg or 20 mg. Placebo controls are included for both the test drug and the challenge drug and the study design is double-blind with crossover. Preliminary data analysis suggests that the nifedipine does not alter the subjective response or reduce the blood pressure and pulse increases observed after a cocaine challenge. It may actually augment them in certain cases. At this writing four subjects have completed the entire study. One to three more subjects are planned for study before terminating this project.

Publications: None

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00004-02 BVL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Human Pharmacology of Cocaine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.H. Jaffe	Acting Chief	BVL, ARC, NIDA
Others:	K. Kumor	Clinical Pharmacologist	BVL, ARC, NIDA
	E. Cone	Section Chief-Chemistry	CDM, ARC, NIDA
	M. Sherer	Psychiatrist - Fellow	BVL, ARC, NIDA
	L. Thompson	Chemist - Fellow	CDM, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Biology of Vulnerability Laboratory, Clinical Biology Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.2	2.6	1.6

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The effects of cocaine in human cocaine using volunteer subjects were studied in order to evaluate physiologic and subjective effects under various pharmacologic conditions.

Continuous Infusion of Cocaine: Tolerance to the subjective and physiologic effects of cocaine has been hypothesized to occur after single i.v. injections of cocaine. Thus, the physiologic and subjective responses of human volunteers during continuous infusions of cocaine which followed bolus injections of cocaine were investigated. This regimen was designed to achieve rapidly a steady-state concentration of cocaine and maintain it. Within limits, this goal was reached and, moreover, compared to the effects obtained with bolus injections of cocaine followed by placebo infusions. The bolus doses were 40 and 60 mg of cocaine, with and without cocaine infusion. Eight subjects were studied. The results indicate: 1) There is no evidence of cardiovascular tolerance to cocaine during continuous infusion; 2) The subjective effects caused by cocaine can be divided into two kinds, those which are cocaine concentration related and those which are not. "Rush" is not related to the cocaine plasma concentration because the experience of rush is unaltered by the cocaine infusion condition; 3) Continuous infusion of cocaine for four hours is associated with a syndrome of feelings of dread, fear of death, paranoia, and hostility. It appears that this syndrome is a prodrome to the paranoid psychosis caused by cocaine.

Repeated Bolus Study: This experiment was designed to study the pharmacologic tolerance to repeated dosing with cocaine. Two intravenous (i.v.) injections of 40 mg of cocaine were given at intervals of 70 minutes or 3 hours and physiologic and subjective effects were studied. The results indicate that at 70 minutes the rush is greatly diminished with reference to the first cocaine injection. However, other subjective effects of cocaine are unchanged. This result is in agreement with the results of experiment A, i.e., these effects are cocaine plasma-dependent but "rush" is not. However, when the interval between injections is 3 hours, the experience of the "rush" returns to the same level as the first injection. Moreover, the other subjective responses have the same magnitude as the initial injection. Thus, it appears that the phenomenon of the "rush" has a refractory period that is re-established within 3 hours. This observation suggests that "rush" may depend on resynthesis of a transmitter.

Publications

Sherer, M.A.: Intravenous cocaine-psychiatric effects, biological mechanisms. J. Biol. Psychiatr., In press.

Sherer, M.A., Kumor, K.M., Jaffe, J.H., Cone, E.J.: Plasma prolactin in experienced cocaine users - A preliminary report. Submitted, August, 1987.

Kumor, K.M., Sherer, M.A., Gomez, J., Cone, E.J. and Jaffe, J.H.: Subjective effects of four-hour cocaine infusions in human volunteers. Submitted, September, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00005-02 BVL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Effect of Naloxone Blockade on Ketocyclazocine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.H. Jaffe	Acting Chief	BVL, ARC, NIDA
Others:	K. Kumor	Clinical Pharmacologist	BVL, ARC, NIDA
	C. Haertzen	Psychologist	BDL, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Biology of Vulnerability Laboratory, Clinical Biology Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Ketocyclazocine is primarily a kappa opiate receptor agonist. In previous work, this group has shown that the drug causes dysphoric effects in opiate-experienced human volunteers (drug abusers). Thus, the goal of this project was to examine the ability of naloxone to block the effects of ketocyclazocine to test the hypothesis that the dysphoria was opiate in nature. Thus, 1.2 mg of ketocyclazocine was administered intramuscularly (i.m.) in combination with 0-5 mg of naloxone. The response of naloxone in combination with 30 mg of i.m. administered morphine was also studied as a control.

The results of this experiment clearly demonstrate naloxone blockade of all the subjective and physiologic effects of ketocyclazocine previously observed. Thus, it appears that these effects are by definition opiate in nature. Furthermore, naloxone is less potent in blocking the effect of ketocyclazocine than morphine; however, the ratio is less than 3/1. This differs from animal experiments in which the ratios observed are 10-20/1. With respect to the status of this work, more statistical analyses need to be conducted and a manuscript prepared.

Addendum 1: Additional work was conducted as an addendum to this original study. It has been postulated that pentazocine, at a low dose, exerts opioid effects by selective stimulation of mu or kappa opioid receptors. At a high dose, however, pentazocine exhibits psychotomimetic effects which may be mediated through its sigma receptor stimulation. Accordingly, one might expect that the analgesic and opioid subjective effects of pentazocine should be naloxone reversible, while the psychotomimetic effects mediated presumably through the sigma receptor should not.

Experimental work was conducted to test this hypothesis. The preliminary results indicate that naloxone blocks all of the subjective, behavioral and physiologic effects of pentazocine. Moreover, extensive interviews, observations of behavior, physical examinations and questionnaires fail to reveal any differences between placebo injections and the combination of pentazocine (70 mg) and naloxone (10 mg) between 0 and 20 minutes post injection of both drugs. Thus, it may be concluded that all the responses measured after pentazocine are opioid in nature. Aside from EEG changes, it was not possible to detect the presence of any activity that might represent sigma activity during this period. Current plans include studying neurohormonal responses after the pentazocine and naloxone combination. Further progress on this protocol awaits availability of staff and facilities to complete this work.

Publications: None

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00006-02 BVL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Comparison of Ketocyclazocine, Morphine, Cyclazocine, Naloxone and Placebo

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	D. Jasinski	Acting Director (now retired)	ARC, NIDA
Others:	K. Kumor	Clinical Pharmacologist	BVL, ARC, NIDA
	C. Haertzen	Psychologist	BDL, ARC, NIDA
	R.E. Johnson	Pharmacist/Chief, Research Support Branch	ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Biology of Vulnerability Laboratory, Clinical Biology Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The effects of the kappa opioid agonist, ketocyclazocine, were compared with the effects of standard opioid drugs in 10 drug-using volunteers. The comparison drugs included cyclazocine, a mixed agonist-antagonist which has a chemical structure similar to ketocyclazocine and is thought to be an agonist of mu, kappa and sigma opioid receptors; morphine, a mu receptor agonist; and naloxone, an opioid antagonist. Subjective and physiologic measures were employed. Moreover, measures of drug identification and judgments of perceived similarity were developed and used.

Ketocyclazocine was found to have properties similar to cyclazocine and to be very different from morphine and naloxone on subjective, identification and judgment measures. Furthermore, the drug exhibited severe dysphoric and hallucinogenic properties. Although these results do not conclusively demonstrate, they do suggest that kappa agonism causes dysphoria or hallucinations.

In this study, the doses of naloxone were between 210 and 300 mg administered i.m. These large doses were employed to assess the subjective effects, prolactin response and physiologic effects associated with high doses of naloxone measured by the recently developed test battery. This work was performed in preparation for kappa agonist blockade studies in which large doses of naloxone will be used to block the effects of kappa receptor agonists. Results of the physiologic, respiration, temperature and prolactin measurements in 10 drug-using volunteers indicate that, at these large doses, naloxone may have some weak opioid agonist activity. Moreover, the results of the subjective report data indicate a vague psychopharmacologic stimulus is present which is compatible with weak agonism at a kappa receptor.

Comparison of Ketocyclazocine, Morphine, Cyclazocine, Naloxone and Placebo

Publications

Kumor, K.M., Haertzen, C.A., Jasinski, D.R., and Johnson, R.E.: The psychopharmacologic and prolactin response after large doses of naloxone in man. Pharmacol. Biochem. Behav., In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00002-03 NEI

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Lexington Addict Followup Study

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.H. Jaffe	Director, ARC	PVL, BVL, ARC, NIDA
Others:	R. Lange	Medical Director	NEI, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Biology

SECTION

NEI

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.1	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A followup study of addicts admitted to Lexington was performed with particular emphasis on testing for the presence of human immunodeficiency virus (HIV). In a cohort of 1129 people admitted to Lexington between 5/71 and 5/72, ELISA testing for HIV virus, with subsequent Western blot confirmation, revealed 29 positive tests. All charts of the cases and 3 random controls for each case have been extracted and the data computerized. To assess mortality, the seropositive cases and 72 seronegative controls were put into the National Death Index, National Center for Health Statistics. Matches were found for 8 of the cases and 27 of the controls (1979-1985) yielding annual death rates of 57/1000 and 56/1000, respectively, as compared with 9/1000 for the mean annual death in the U.S. over the same period. Even though the death rates were high, there was not excess mortality in the seropositive versus the seronegative members of the cohort. No data on death in the cohort between 1972-1979 are yet available, although this period is when cases of AIDS are likely to have succumbed. Supplementary Social Security statistics are being collected.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA00003-02 NEI

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

HIV Seroprevalence Pilot Study - Geographic

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.H. Jaffe	Director, ARC	PVL, BVL, ARC, NIDA
Others:	R. Lange	Medical Director	NEI, ARC, NIDA
	E. Dax	Laboratory Chief	NEI, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

NEI

SECTION

Clinical Biology Branch

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.1	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

An Addiction Research Center Epidemiology Collaborating Group was established and a seroprevalence survey of HIV antibodies in intravenous drug users (IVDUs) was conducted in six distinct regions of the country. After obtaining informed consent, 1,770 IVDUs were studied. The wide disparities in HIV seroprevalence in the face of similarities in drug-using behavior have important implications for prevention. In the New York City area (Harlem, Brooklyn), 61% of samples obtained in late 1986 were positive, up from 50% of samples from the same program taken in early 1985. In Baltimore, 29% of samples, from 11 programs, were positive.

In contrast, samples from programs distant from the Northeast corridor had far lower rates: Denver, 5%; San Antonio, 2%; Southern California, 1.5%; Tampa, 0%. In New York, there was no difference between Harlem and Brooklyn; among the Southern California communities, only the following areas had positive results: metropolitan Fresno, 6%; metropolitan Los Angeles, 2%; and communities from Santa Monica to Oxnard, 2%. Besides geographic location, the only surveyed variable associated with seropositivity in this study was ethnicity, with HIV antibodies being much more common in Blacks and Latinos than in Whites.

Contrary to expectations, there was no corresponding difference in lifetime needle sharing experience among the IVDUs in the regions studied. The duration of street drug use was similar between sites, with a median period of 18.5 years, and the prevalence of needle-sharing ranged from 70% in New York to 99% in San Antonio. Because needle-sharing is practiced by IVDUs in areas where seroprevalence is still relatively low, these areas are potentially vulnerable to the same catastrophic spread seen in the Northeast. However, a window of opportunity exists in which prompt, vigorous, and aggressive efforts at prevention could have major impact. To continue the survey through 1988, samples from the same areas are being collected.

Z01 DA 00003-02 NEI

HIV Sero-Prevalence Pilot Study - Geographic

Publications - FY 1987

Lange, W.R., Snyder, F.R., Lozovsky, D., Kaistha, V., Kaczaniuk, M.A., and Jaffe, J.H.: The geographic distribution of human immunodeficiency virus markers in parenteral drug abusers. Am. J. Public Health, In press.

Lange, W.R., Cone, E.J., and Jaffe, J.H.: The prevalance of hepatitis B and human immunodeficiency virus markers in a sample of Haitian entrants. Public Health Rep., In press.

Lange, W.R.: Viral hepatitis and international travel. Am. Fam. Phys. 36: 179-184, 1987.

Lange, W.R., and Dax, E.M.: Human immunodeficiency virus infection and international travel. Am. Fam. Phys., In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00004-02 NEI

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Inhalable Nitrites - Abuse Potential and Immune Function

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.H. Jaffe	Director, ARC	PVL, BVL, ARC, NIDA
Others:	E. Dax	Laboratory Chief	NEI, ARC, NIDA
	R. Lange	Medical Director	NEI, ARC, NIDA
	R. Herning		CHP, ARC, NIDA
	R. Litow		NEI, ARC, NIDA
	N. Robinson		NEI, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

NEI

SECTION

Clinical Biology Branch

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.1	0.25	0.75

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The intake and frequency of inhalation of inhalable nitrites has been associated with the incidence of Kaposi's sarcoma in people suffering from AIDS. Animal and in vitro studies have shown that immune cell function can be altered by these agents. However, no study directly relating the effects of nitrites to disturbances of immune function has been performed in humans. Thus, a study has been designed and conducted using healthy, HIV negative volunteers. An inhalation protocol in which the subject inhales 3 doses of amylnitrite for 3 days and 1 dose on the fourth day is being conducted. A battery of immune function tests is carried out on 2 occasions prior to the inhalation protocol, immediately following the last dose, and at 24 hours, 96 hours, and 7 days after the last dose. The subjects exhibited a decrease in white cell counts at days 1-2 which was reflected in reduced T-cell counts. By day 7, the white cell count had returned to, and possibly overshot, baseline levels. Natural killer cell activity was impaired in the first 24 hours following inhalation and returned to baseline by 4 days. Alternatively, there was an augmented response to T-cell mitogens by 7 days following drug but no change in response between days 1-4. Thus, exposure to nitrites over the four days showed initial immune suppression followed by a non-specific immune-stimulation. This pattern may be altered by chronic, repeated exposure to the inhalant. Thus, another group of subjects has been exposed to nitrites in the same manner as the first group and then exposed to two additional doses per week for 2 additional weeks. The results are being analyzed. Similar studies with the more commonly abused isobutylnitrite will be carried out.

Since little is known about the abuse potential of the nitrites, the protocol includes tests of this potential. Results of these tests, along with results of cognitive function tests and EEG studies, are currently being analyzed.

Z01 DA 00004-02 NEI

Inhalable Nitrites - Abuse Potential and Immune Function

Publications - FY 1987

Dax, E.M., Adler, W.H., Nagel, J.E., Lange, W.R. and Jaffe, J.H.: Effects of nitrites on the immune system of humans. NIDA Research Monograph Series, In press.

Lange, W.R., Haertzen, C.A., Hickey, J.E., Snyder, F.R., Dax, E.M. and Jaffe, J.H.: Nitrite inhalants, contemporary patterns of abuse. Am. J. Alc. Drug Abuse, In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA00005-01 NEI

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
HIV Prevalence: In Depth Survey of Baltimore

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: J.H. Jaffe	Director, ARC	PVL, BVL, ARC, NIDA
Others: R. Lange	Medical Director	NEI, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH
NEI

SECTION
Clinical Biology Branch

INSTITUTE AND LOCATION
Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.25	0.25

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The seroprevalence of HIV antibodies in surveyed intravenous drug users (IVDUs) who were either recently enrolled into treatment or were on a waiting list for enrollment was 29%. The rate among ARC research subjects with parenteral drug use histories has averaged 24%, and among area prostitutes with heavy drug use histories, 34%. In Baltimore, 94% of IVDUs had shared needles, and even though HIV seropositivity was not associated with a needle-sharing history, there was an association between the intensity of sharing and the probability of being seropositive. A much stronger association was observed between seropositivity and "shooting gallery" visitation, suggesting that this milieu of sharing, rather than other environments, is the real risk factor.

Very distinct ethnic group differences in HIV infection were observed, with Blacks being much more likely to be seropositive than Whites (odds ratio = 8.18, 95% CI 3.35-19.97). There was no significant difference in HIV infection between Blacks in Baltimore and in New York City. Shooting gallery visitation appears to be much more a phenomenon among Black IVDUs than it is in Whites ($X^2 = 8.23$, $p<0.01$). HIV infection has appreciably penetrated Baltimore's addict community. The overall seroprevalence rate in Baltimore in 1986 (29%) approximated that of New York in 1979 (27%) where the rate subsequently jumped to 58% in some areas by 1984 and has increased to 60% in 1987.

The survey will be continued through 1988.

Z01 DA 00005-01 NEI

HIV Prevalence: In Depth Survey of Baltimore

Publications - FY 1987

Lange, W.R., Snyder, F.R., Lozovsky, D., Kaistha, V., Kaczaniuk, M.A. and Jaffe, J.H.: HIV infection in Baltimore: Antibody seroprevalence rates among parenteral drug abusers and prostitutes. Maryland Med. J., In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00006-01 NEI

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cannabinoids and Their Effects on the Immune System and Cognitive Function

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.H. Jaffe	Director, ARC	PVL, BVL, ARC, NIDA
	E.M. Dax	Laboratory Chief	NEI, ARC, NIDA
Others:	R. Lange	Medical Director	NEI, ARC, NIDA
	R. Litow		NEI, ARC, NIDA
	N. Robinson		NEI, ARC, NIDA

COOPERATING UNITS *(if any)*

William Adler, M.D., Gerontology Research Center

LAB/BRANCH

NEI

SECTION

Clinical Biology Branch

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
	0.25	0.75

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Delta-9-tetrahydrocannabinol (THC) has been hypothesized to influence immune function. However, this has not been investigated in a comprehensive fashion in humans. The purpose of this study is to measure and study the temporal effects of THC on immune function. The effects of THC on cognitive function will also be investigated. Experienced substance abusers, who are heavy users of THC, will be recruited. Immune function will be investigated during the excretion phase, during administration of orally administered THC and during the second washout phase.

Since THC is often used with nitrites (see project #Z01 DA00004-02 NEI), the effect of THC administration together with nitrites will be examined in a subsequent study.

Blood will be drawn for hormone estimation in these studies in order to correlate immune responses with changes in hormone secretion. Any possible endocrine-immune function links will be followed up in animal studies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00007-01 NEI

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Hormonal Diurnal Rhythms During Cocaine Withdrawal

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	E. M. Dax	Laboratory Chief	NEI, ARC, NIDA
Others:	W. Weddington		TEI, ARC, NIDA
	N. Pilotte		NEI, ARC, NIDA
	J.H. Jaffe	Director, ARC	PVL, BVL, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

NEI

SECTION

Clinical Biology Branch

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.1	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Cocaine withdrawal (and withdrawal from other drugs) is associated with sleep disturbances. Whether the sleep disturbances are related to the life-style of cocaine abusers (in a situation similar to jet lag) or diurnal rhythms are disturbed secondary to disturbances of dopamine function has not been determined. In men known to be cocaine abusers, the diurnal rhythms of hormones regulated by dopamine (prolactin and growth hormone), as well as others not under dopaminergic control, will be examined during cocaine withdrawal. Since sleep disturbances are one of the more uncomfortable aspects of cocaine withdrawal, the imposition of hormonal rhythms may facilitate more comfortable withdrawal. The study may provide further information on dopaminergic control of hormonal secretion and its role in maintaining diurnal rhythms of hormones.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA00008-01 NEI

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Effects of Cocaine on Hormone Secretion from the Anterior Pituitary

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: N. Pilotte		NEI, ARC, NIDA
Others: E. Dax	Laboratory Chief	NEI, ARC, NIDA

COOPERATING UNITS *(if any)*

Carlo Contoreggi	Endocrine Section	GRC
Marc Blackman	Endocrine Section	GRC

LAB/BRANCH

NEI

SECTION

Clinical Biology Branch

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.2	0.1	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Tolerance to the physiologic effects of cocaine may occur after as little as a single dose of cocaine. At least part of this effect is dopamine mediated. Prolactin, an anterior pituitary hormone, is regulated by dopamine which is released from a discrete population of neurons within the medial basal hypothalamus. Thus, dopamine release in the male rat is an indirect measure of dopamine release. Dopamine will also be quantitated directly in some experiments.

Secretion patterns will be examined using several techniques now established in this Laboratory. Direct secretion of dopamine will be examined in the hypothalamo-portal blood of live anesthetized animals before and after acute cocaine treatment and, subsequently, in rats treated with cocaine for varying periods of time. In isolated pituitaries and hypothalami, perifused alone or in tandem, the output of dopamine and neuropeptides will be examined concomitantly with the release of prolactin to examine release not under the influence of higher centers. Finally, prolactin release will be examined in dispersed anterior pituitary cells to assess cocaine's effects on secretion at the cellular level.

Thus, the role of the dopaminergic system in cocaine tolerance and the use of prolactin as an accurate marker for dopaminergic function will be studied in cocaine treated animals.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00009-01 NEI

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Mobilization of Pools of Peptide Hormone as a Function of Drug Environment

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: N. Pilotte		NEI, ARC, NIDA
Others: E. Dax	Laboratory Chief	NEI, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

NEI

SECTION

Clinical Biology Branch

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.25	0.25

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Cocaine and other drugs release prolactin from one of at least two intracellular pools in normal pituitary cells cultured in the absence of dopamine. In addition, studies examining release of prolactin by thyrotropin releasing hormone suggest that there are different populations of lactotropes which may release prolactin by different stimulators or mechanisms. Prolactin will be quantitated in a reverse hemolytic plaque assay. Autoradiographic techniques will be employed to decipher which pool of prolactin is released from lactotropes in response to various stimulators in the presence and absence of dopamine.

It is hoped that these experiments will contribute to deciphering at which level or levels drugs interact with the hypothalamo-pituitary system.

GPO 814-818

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00010-01 NEI

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Metabolism of Tripelennamine and Pyrilamine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: S.Y. Yeh Pharmacologist NEI, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

NEI

SECTION

Clinical Biology Branch

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Tripelennamine, an antihistamine, has been abused in combination with pentazocine, a narcotic agonist/antagonist. The purpose of this study is to determine the effect of pentazocine on the urinary metabolic profile of tripelennamine. The major metabolite of tripelennamine in rats was found to be 4-hydroxytripelennamine in both free and conjugated forms. After administration of drug, urine was collected, hydrolyzed with gluculase and extracted with benzene-isopropanol. Extracts were analyzed by TLC, GC, and GC/MS. In man, free and conjugated alpha-hydroxytripelennamine was the major metabolite of tripelennamine. Tripelennamine, N-glucuronide conjugated tripelennamine, and total (free plus conjugated) alpha-hydroxytripelennamine in the 24 hour human urine was 1.2%, 4.5%, and 23% of the administered dose (100mg, i.m.), respectively.

In the 24 hour urine of male rats administered tripelennamine, the amount of tripelennamine and its metabolites, 2-(2-dimethylaminoethyl)aminopyridine in free form, alpha-hydroxytripelennamine, 4-hydroxytripelennamine, 2-[4-hydroxy-3-methoxybenzyl-(2-dimethylaminoethyl)amino]pyridine and 2-[3-hydroxy-4-methoxybenzyl-(2-dimethylaminoethyl)amino]pyridine in conjugated form were found to be 1.4%, 3.0%, 7.5%, 3.7%, 0.3%, and 0.2% of the administered dose, respectively. A similar pattern was seen in female rats. In the 24 hour urine of male rats administered pyrilamine, the amount of pyrilamine and its metabolites, 2-(2-dimethylaminoethyl)aminopyridine in free form, 4-hydoxytripelennamine, 4-hydroxydesmethyltripelennamine, 2-[4-hydroxy-3-methoxybenzyl-(2-dimethylamino-ethyl)amino]pyridine and 2-[3-hydroxy-4-methoxybenzyl-(2-dimethylaminoethyl)-amino]pyridine in the conjugated form were found to be 1.75%, 0.5%, 25%, 7.5%, and 1.00% of the administered dose, respectively. The respective metabolites in the urine of female rats were 1.20%, 0.5%, 47%, 15%, and 2.0%. These metabolites represented less than 0.5% of the administered dose in the 48 hour urine.

Z01 DA 00010-01 NEI

Metabolism of Tripelennamine and Pyrilamine

Publications - FY 1987

Yeh, S.Y.: N-debenzylation of pyrilamine and tripelennamine in the rat; A new metabolic pathway. Drug Metab. Dispos. 15: 466-472, 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00011-01 NEI

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effect of MDA and MDMA on Dopamine and Serotonin in the Rat Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	S.Y. Yeh	Pharmacologist	MPL, ARC, NIDA
Others:	G. Battaglia	Staff Fellow	MPL, ARC, NIDA
	E.B. DeSouza	Visiting Scientist	MPL, ARC, NIDA
	M.J. Kuhar	Branch Chief	MPL, ARC, NIDA

COOPERATING UNITS *(if any)*

Department of Defense, U.S. Army (F.-L. Hsu)

LAB/BRANCH

NEI

SECTION

Clinical Biology Branch

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.4	0.4	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

MDA and MDMA deplete serotonin content and destroy serotonergic neurons when these drugs are administered s.c. but do not show the neurotoxic effects when administered intracerebrally. The purpose of the present study was to investigate the effect of the dose of MDMA and the length of treatment on serotonergic function. Recovery of function after administration of MDMA, 20 mg/kg s.c., twice daily for 4 days was also followed. Also, the neurotoxic effect of MDMA in different species and the effects of a serotonin uptake inhibitor, a drug metabolism enzyme inhibitor, and chlorpromazine were investigated. The neurotoxic effects of MDA and MDMA were also compared with their metabolites.

Repeated systemic administration of various doses of MDMA (5-20 mg/kg twice daily for 4 consecutive days) resulted in dose-dependent decreases in 5-HT, 5-HIAA and 5-HT uptake sites. Increasing the number of injections of MDMA resulted in progressively greater reductions in 5-HT and 5-HIAA. Pretreatment with the serotonin uptake inhibitor citalopram prior to each injection of MDMA prevented the neurotoxic effects of MDMA on the 5-HT parameters described above, but the inhibitor of cytochrome P-450 metabolism SKF-525A did not. The neurotoxic effects of MDMA were observed in the rat and guinea pig but no significant changes occurred in brains of mice.

4-hydroxy-3-methoxyamphetamine was synthesized. The neurotoxic effects of 4-hydroxy-3-methoxyamphetamine and alpha-methyldopamine (metabolites of MDA) were less than that of MDA. The toxicity of alpha-methylnorepinephrine, another metabolite of MDMA, was higher than that of MDA. In addition, pretreatment with the neuroleptic chlorpromazine did not alter MDMA-induced neurotoxicity on various brain 5-HT parameters.

Z01 DA 00011-01 NEI

Effect of MDA and MDMA on Dopamine and Serotonin in the Rat Brain

Publications - FY 1987

Battaglia, G., Yeh, S.Y., O'Hearn, E., Molliver, M.E., Kuhar, M.J., and DeSouza, E.B.: 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxyamphetamine (MDA) destroy serotonin terminals in rat brain: Quantification of neurodegeneration by measurement of ^{3}H-paroxetine-labeled serotonin uptake sites. J. Pharmacol. Exp. Ther., In press.

Battaglia, G., Yeh, S.Y. and DeSouza, E.B.: MDMA induced neurotoxicity: Parameters of degeneration and recovery of brain serotonin neurons. Pharmacol. Biochem. Behav., In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00012-01 NEI

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effect of Cocaine on Monoamines and their Metabolites in the Brain of Rats

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: S.Y. Yeh Pharmacologist MPL, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

NEI

SECTION

Clinical Biology Branch

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.4	0.4	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this study is to determine the effects of acute and short-term cocaine treatment on neurotransmitters, particularly monoamines and their metabolites, GABA and tyrosine hydroxylase. Rats were injected either s.c. or i.p. with cocaine, 20 mg/kg, or saline every 12 hours for 8 days. Motor activities after the first injection of cocaine was measured and found to be increased over controls. After s.c. injection, cocaine increased motor activity more slowly with peak activity at 3 to 4 hours. Twenty-four hours after the last injection, the animals were sacrificed by decapitation. The brain and adrenal glands were removed. Monoamines and their metabolites, as well as gamma-aminobutyric acid (GABA) and tyrosine hydroxylase activity were measured. Cocaine increased hypothalamic content of norepinephrine (NE) by 133% and 100%, dopamine (DA) by 177% and 120%, 3,4-dihydroxyphenylacetic acid (DOPAC) by 68% and 13% and homovanillic acid (HVA) by 77% and 58% after s.c. and i.p. injection, respectively, as compared to saline controls. The content of GABA and tyrosine hydroxylase activity are being measured. Ongoing studies will further investigate the acute effects of cocaine on these parameters in other anatomical areas.

GPO 914-918

Z01 DA 00012-01 NEI

Effect of Cocaine on Monoamines and Their Metabolites in the Brain of Rats

Publications - FY 1987

Yeh, S.Y.: Effects of repeated cocaine administration on brain monoamines in rats. Fed. Proc. 46: 404, 1987.

Preclinical Pharmacology Branch

Steven Goldberg, Ph.D., Chief

The Preclinical Pharmacology Research Branch conducts research on the behavioral modes of action of drugs both in producing reinforcing, punishing and discriminative stimuli, and in altering established behavior controlled by non-drug events such as food or electric shock. It also studies the neural circuits involved in the action of drugs of abuse and the role of genetics in determining the effects of drugs of abuse. Studies cover a wide range of topics, including the pharmacology of opioid and cocaine dependence, alterations in the acquisition and retention of classically conditioned behavioral and physiological responses by drugs of abuse, and environmental and genetic determinants of drug-seeking and drug-taking behavior. The Branch also conducts neuropsychopharmacology research using animal models to investigate the modes of action of drugs of abuse, the neurobiologic basis of reinforcement, and pathologic changes in neural function that predispose to, or are a consequence of, drug abuse. Research is carried out in both primates and non-primates. New drugs are evaluated for abuse potential by comparison of reinforcing, aversive and discriminative stimulus effects and by comparison of effects of prototypic drugs of abuse on neurophysiologic systems. The Preclinical Pharmacology Research Branch consists of two laboratories (see below).

Behavioral Pharmacology and Genetics Laboratory - Steven R. Goldberg, Ph.D., Chief

1. Section on Behavioral Pharmacology

Overview

The Behavioral Pharmacology Section of the Behavioral Pharmacology and Genetics Laboratory is responsible for research on the reinforcing effects of drugs of abuse, the influence of such drugs on learned operant behavior, and the discriminative stimulus effects of these drugs. The roles of drugs of abuse from four different pharmacological classes, including psychomotor stimulants, opioids, sedative/hypnotics, and benzodiazepines, are being investigated with respect to how the opportunity for occasional drug self-administration leads to long sequences of integrated behavior culminating in self-administration of the drug and how administration of these drugs alters ongoing behavior controlled by non-drug events such as food or water presentation or electric shock delivery.

The positive reinforcing as well as the punishing properties of these drugs are being studied to develop an understanding of how drug-seeking behavior becomes strong and persistent and how it might be weakened by pharmacologic and behavioral means. These objectives are pursued using a variety of experimental procedures, including (1) assessing the reinforcing effects of these drugs using intravenous self-administration procedures, (2) examining

their effects as noxious stimuli using schedules of punishment of ongoing behavior by i.v. drug injections or schedules of termination or postponement of i.v. drug injections, (3) quantifying the behavioral effects using fixed-interval and fixed-ratio schedules of food presentation or electric shock delivery or postponement as baselines, and (4) determining their effects as discriminative stimuli using two-lever choice situations.

Collaborative studies are being pursued with other laboratories at the ARC. For example, collaborative studies of neurochemical correlates of the behavioral actions of psychomotor stimulants are being pursued with the Neuroscience Branch utilizing studies of receptor binding and local cerebral glucose utilization. Comparative studies of repeated sequences of drug-seeking behavior controlled by i.v. or i.m. administration of various doses of cocaine, morphine or placebo under complex second-order schedules in humans and in non-human primates are being pursued jointly with the Biology of Dependence and Abuse Potential Assessment Laboratory.

The long-term goals of the Behavioral Pharmacology Laboratory continue to focus on environmental conditions which determine whether drugs have positive reinforcing or aversive effects, on the use of complex second-order schedules of drug injection in humans and non-human primates to investigate the control of drug-seeking behavior by associated environmental stimuli, and on determination of the pharmacological mechanisms of the behavioral effects of drugs of abuse. Some immediate specific aims are:

To analyze mechanism of reinforcing actions of cocaine by assessing the effects of a series of cocaine metabolites and analogs as reinforcers and as modifiers of schedule-controlled behavior, correlating these behavioral effects with biochemical actions.

To investigate reinforcing effects of cocaine and morphine using second-order scheduling procedures that minimize cumulative effects of successive injections and allow a dissociation of reinforcing from other behavioral effects of the drug. These procedures provide unique baselines for: (1) investigating the role of environmental stimuli previously associated with drug injection in sustaining drug-seeking behavior when drug is no longer available, (2) comparing the reinforcing effects of opioids and drugs acting through non-mu receptor mechanisms, and (3) cross validating human and animal models of drug abuse.

To delineate conditions under which tolerance develops to the behavioral and physiological effects of cocaine and to characterize any withdrawal syndrome that unfolds after chronic administration.

To further characterize the supersensitivity that develops to opiate antagonists with respect to pharmacological specificity, time course of development and recovery.

To investigate the pharmacological specificity of opioid effects on associative learning processes through the use of drugs with specific actions at mu, kappa, sigma and delta receptors.

To characterize receptor specificity of anxiogenic drugs and benzodiazepine antagonists using schedule-controlled behavior and to delineate mechanisms of anxiogenic action when these drugs function as punishing stimuli.

To determine mechanisms of overlapping behavioral effects of nicotine and anxiogenic beta-carbolines.

Summary of Ongoing Research

Project: Maintenance of Behavior by Drug Injections.
Investigators: S.R. Goldberg, J.L. Katz, and C.W. Schindler

Drugs of abuse can come to control large amounts of behavior by acting as either reinforcing stimuli to maintain behavior that leads to their administration, or by functioning as discriminative stimuli that are associated with conditions under which behavior is consistently reinforced by other relevant stimuli, such as presentation of food or avoidance of electric shock. In many situations, drugs of abuse probably function through multiple mechanisms to persistently sustain long sequences of drug-seeking behavior that may be very resistant to extinction. Schedule-controlled performances provide a meaningful way to analyze these long sequences of drug-seeking behavior in the same way as operant behavior maintained by other events such as food or electric shock.

In one series of experiments with squirrel monkeys and rhesus monkeys, the rates and patterns of responding maintained by various drugs, including cocaine, nicotine, caffeine, methohexital, morphine and chlordiazepoxide are being compared using simple fixed-ratio and fixed-interval schedules as well as complex second-order schedules with brief stimulus presentation in which the role of brief stimuli in maintaining extended sequences can be assessed. Studies of the effects of presession treatments with a range of doses of pharmacologic agonists and antagonists, such as caffeine, specific D-1 and D-2 dopamine antagonists, serotonergic reuptake inhibitors, and alpha-adrenergic antagonists, on responding maintained by i.v. psychomotor stimulant injection or food presentation under fixed-interval, fixed-ratio and second-order schedules will be continued. These experiments with long second-order schedules in which drug is injected only at the end of the session will be extended to study the reinforcing effects of other drugs, including benzodiazepines and barbiturates. Studies of pharmacological and environmental means of weakening established behavior maintained by different drugs will also be continued.

Several studies have indicated that certain hallucinogens from the series of phenalkylamines can function as reinforcers, whereas others do not. Recent attention has focused on this group of drugs as a result of the popularity of d,l-3,4-methylenedioxymethamphetamine (MDMA). However, due to the

development of designer drugs, there is interest in all of the structural variants of this compound. From studies of drug discrimination, it is known that both MDMA and MDA, but not several other ring-substituted phenalkylamines, have discriminative effects similar to those of d-amphetamine. These results suggest that the lack of reinforcing effects of certain hallucinogens is not due to serotonergic activity, but rather is due to a lack of a critical action, such as an amphetamine-like effect. This possibility will be examined by conducting structure-activity studies of reinforcing effects of phenalkylamines.

There is currently an ongoing study examining the structure-activity relationships between self-administration of the stereoisomers of cocaine and a variety of cocaine-like compounds and their action in displacing mazindol binding. Data from this study will be useful in cross-procedure correlation; that is, it may provide a way of validating results obtained using biochemical and molecular experimental approaches. In this study, squirrel monkeys respond under a fixed-ratio 30-response schedule of intravenous drug injection with a time-out 300-sec. Experimental sessions are conducted each weekday and at session's end after one hour or 12 injections, whichever comes first. Baseline responding is maintained with 56 pg/kg/injection of cocaine. On Tuesdays and Fridays, doses of the test drugs or saline are substituted for the baseline dose of cocaine.

Saline substitutions maintain only very low levels of self-administration. The following potency order was obtained l-cocaine > norcocaine > d-pseudococaine > d-cocaine = l-pseudococaine = inactive. These potencies correlate well with those obtained using receptor binding techniques. When sufficient quantities of the cocaine analogs WIN 35,065-2, WIN 35,065-3, WIN 35,981 and WIN 35,428 are available, these compounds will be studied, once again in collaboration with the Neuroscience Branch.

In a series of discrimination studies, squirrel monkeys were trained to discriminate i.v. injections of l-nicotine from saline. Once reliable discriminative control was established with l-nicotine, subjects were tested with other doses of l-nicotine, d-nicotine, l-nornicotine, and l-cotinine. The order of potency of the drugs was l-nicotine > l-nornicotine = d-nicotine >> l-cotinine. The potency of l-cotinine could be accounted for entirely by the l-nicotine impurity in this preparation. Previous studies of the psychomotor stimulant effects of these compounds in squirrel monkeys have found increases in response rates under fixed-interval schedules with l-nicotine and l-cotinine, which were approximately equipotent, but not with d-nicotine. The present results suggest that the effects of l-cotinine are not mediated by nicotinic mechanisms and that nicotinic agonist action alone (e.g., d-nicotine) is not sufficient activity for a psychomotor stimulant effect. These studies are continuing by examining the overlapping discriminative effects of nicotine and beta-carbolines. Preliminary results suggest that the discriminative effects of nicotine and related compounds may involve mechanisms similar to those involved in the aversive effects of drugs.

Project: Behavioral Pharmacology of Non-Opioid Analgesics.
Investigators: S.R. Goldberg and M.D. Swedberg

In a series of discrimination studies, rats were trained to discriminate intraperitoneal injections of either flupirtine (10.0 mg/kg) or D-16949 (2.0 mg/kg), non-opioid analgesics in clinical use or in clinical trials in Europe, from the no drug condition in a two choice shock avoidance procedure. Avoidance of electric shocks was contingent upon whether or not the training drug had been injected prior to the session. Putative agonists were substituted for the training drug, and putative antagonists were administered in combination with the training drug, respectively. Results indicate alpha-2 adrenergic mechanisms to be of primary importance in mediating the discriminative effects of flupirtine. Opiate mechanisms have been eliminated on the basis of non-substitutability of opioid analgesics and lack of effect of the opiate antagonist naltrexone. With D-16949, tests with opioid analgesics, phencyclidine, d-amphetamine and LSD indicate lack of similarities in discriminative effects. Tests with serotonergic agonists and antagonists indicate that 5-HT_{1B} mechanisms probably are of primary importance in mediating the discriminative effects of D-16949.

Project: Suppression of Behavior by Drug Injections.
Investigators: J.L. Katz, S.R. Goldberg

Many psychoactive drugs, including cocaine, nicotine and nalorphine, exhibit an important quality shared with certain other types of stimuli. That is, they can function effectively as positive reinforcers or as punishers within the same dose range depending on the context of environmental conditions. Systematic evaluation of the environmental conditions which determine the type and direction of behavioral effects with a variety of drugs may have practical implications for the control of licit or illicit drug use by humans. Initial studies in this project demonstrated that nicotine can function either as a reinforcer to maintain behavior, or as a punisher (aversive or noxious stimulus), to suppress behavior, depending on the context in which it is administered. It is the object of this project to extend these studies to additional drugs under a variety of conditions. Responding will be maintained by food presentation in the presence of either of two distinctive visual stimuli. Responses will occasionally produce drug injections in addition to food only in the presence of one of the stimuli (punishment component). Drugs will be studied in squirrel and rhesus monkeys to determine if they selectively suppress responding only in the punishment components of the schedule.

Initial studies have now been conducted with several drugs. In the first studies, previous effects with histamine and nicotine have been replicated using the current procedures which are modifications of the ones used previously. In subsequent studies, a variety of drugs has been examined in an attempt to screen drugs that may be of future interest. Punishing effects have been indicated for: ethyl-B-carboline-3-carboxylate, buspirone, gepirone, yohimbine, and quipazine. Drugs that appear to lack specific punishing effects under this procedure are: cocaine and midazolam.

Interesting results will be followed by a more complete pharmacological analysis of effects.

Project: Behavioral Effects of Opioid Agonists, Opioid Mixed Agonist-Antagonists, and Other Drugs of Abuse in Pigeons, Squirrel Monkeys and Rhesus Monkeys.
Investigators: J.L. Katz, S.R. Goldberg, and C.W. Schindler

This project is designed to provide a characterization of the reinforcing effects of opioid agonists, mixed agonist-antagonists and opioid antagonists. These studies will examine the effectiveness of these drugs as reinforcers under conditions allowing for a dissociation of their reinforcing effects from their other pharmacological effects. Moreover, these studies will examine the role of environmental stimuli that are occasionally associated with drug injection in the facilitation of drug-seeking behavior and its resistance to extinction. Additionally, the interactions of narcotic antagonists with opioid-maintained behavior and their acute and chronic effects on behavior maintained by food presentation in non-dependent and morphine-dependent rats and monkeys will be explored.

The reinforcing effects of opioids were assessed in squirrel monkeys trained to respond for i.v. injections of morphine or fentanyl under second-order schedules of reinforcement. These effects were compared to monkeys trained under identical schedules, but with food as the reinforcer. Under these schedules, each 30th response produced the stimulus and the stimulus was intermittently paired with an injection of drug or the presentation of food. Both drugs effectively maintained responding with this procedure. Food reinforcement maintained an amount and pattern of behavior similar to that of the opioids. Following initial training, the removal of either morphine or food reinforcement failed to reduce behavior. This effect was determined to be due to the visual stimuli which were presented throughout the session. When these stimuli were removed, the animals stopped responding. Responding initially increased, but subsequently decreased when the stimuli were re-introduced. Moreover, re-introduction of morphine or food increased the level of behavior to initial values. Subsequently, removal of morphine or food decreased behavior even in the presence of the brief stimuli. These studies will be followed up by studying the reinforcing effects of opioids thought to interact with the kappa and sigma receptors. Any further interesting behavioral or pharmacological effects will be followed up appropriately.

With the second-order schedule described above, naltrexone blocked the ability of morphine, but not food, to maintain behavior. In addition, a profound supersensitivity to naltrexone developed. Initially, a dose of 3 mg/kg naltrexone was required to decrease rates of responding maintained by morphine. However, after repeated acute dosing (1/week), a dose as low as 0.03 mg/kg was effective. A similar phenomena has been observed in rats responding for food, but at much higher doses. Initially a dose of 100 mg/kg naltrexone was required to affect response rate. After a period of 4 weeks when 100 mg/kg/week naltrexone was administered, a dose of 10 mg/kg naltrexone began to affect behavior and a dose of 30 mg/kg has an effect

similar to the effect 100 mg/kg had in the first week. These studies will be followed up examining the effects of chronic naltrexone administration, the interaction of chronic morphine administration with naltrexone administration, and the interaction of potential antagonists with these effects (e.g., chlordiazepoxide).

The significance of these findings is three-fold. First, opioids can maintain a long chain of behavior which would be analogous to the ritual behavior necessary for the human addict to obtain and administer abused drugs. Second, the results of the manipulations of environmental stimuli suggest the importance of these stimuli in maintaining drug-seeking behavior and of incorporating the effects of environmental stimuli in any drug treatment program. Finally, with the use of naltrexone in drug treatment programs, these studies suggest the possibility that the effects of these drugs on behavior may increase with continued administration.

Project: Effects of Drugs on Schedule-Controlled Behavior of Experimental Animals.
Investigators: S.R. Goldberg and J.L. Katz

General information on the behavioral pharmacology of a drug in the pertinent species is necessary to evaluate quantitatively how the drug functions as a reinforcer or a punisher and to establish a profile of behavioral effects. Multiple schedules of food presentation with both fixed-interval and fixed-ratio components have been most frequently used in this type of study since they generate a wide range of rates and patterns of responding within a session and provide stable, long-term baselines for chronic studies in individual animals. The present project involves the assessment under multiple schedules of food presentation in squirrel monkeys, rats, and pigeons of both the acute and chronic effects of a variety of drugs, including psychomotor stimulants, such as cocaine, various cocaine analogs, nicotine and caffeine, various narcotic agonists and antagonists, and benzodiazepine agonists and antagonists. Because the behavioral effects of certain drugs depend on the type of event that maintains behavior, the effects of drugs on comparable performances maintained by either delivery of electric shock or by termination of a stimulus associated with electric shock also are studied. These procedures provide stable, long-term, sensitive baselines for quantitative assessment of both stimulant and depressant drug effects.

The long-term nature of these baselines also makes them ideal for studying tolerance and cross-tolerance development to chronic treatment with various drugs, including cocaine, caffeine, adenosine analogs, and benzodiazepines. These procedures result in comparable rates and patterns of behavior in different species of experimental animals. Since a large body of literature on the effects of a variety of drugs from many pharmacologic classes already exists for comparison, these procedures are valuable for assessing the behavioral pharmacology of other compounds, such as cocaine metabolites and analogs, nicotine-like agonists, narcotic agonists and antagonists, B-carbolines and benzodiazepine antagonists.

Studies on the effects of various cocaine analogs on schedule-controlled behavior are underway either as an extension of a series of collaborative studies with the Neuroscience Branch or to follow up on interesting results from previous studies. The studies are being conducted to provide additional information on the structure-activity relationship of cocaine-like compounds. This information will permit correlation of results across levels of analysis ranging from behavioral to molecular.

Studies are being conducted in pigeons and squirrel monkeys responding under multiple fixed-interval 600-sec, fixed-ratio 30-response schedules of food presentation and squirrel monkeys responding under a fixed-ratio 30-response, time-out 300-sec schedule of food presentation. The later schedule is identical, except for the maintaining event, to the schedule used in the drug self-administration studies of these compounds. Studies under the multiple fixed-interval, fixed-ratio schedule are just getting under way, while studies under the fixed-ratio, time-out schedule are nearly complete. Results from this later study indicate that the order of potency for the compounds suppressing fixed-ratio responding is l-cocaine > norcocaine > d-pseudococaine = l-pseudococaine > d-cocaine, which correlates well with self-administration and receptor binding information. These studies are continuing with a focus on other cocaine-like compounds previously tested in the Neuroscience Branch and on a group of Winthrop-Sterling cocaine analogs currently being synthesized under contract (e.g., WIN 35,428, WIN 35,065).

Studies of the effects of a series of benzodiazepine antagonists were conducted in nontolerant and chlordiazepoxide-tolerant rats. These studies showed that supersensitivity developed to the effects of the antagonists, Ro15-1788, CGS-9895, and B-CCT, but not to ethyl-B-carboline-3-carboxylate. Additionally, obvious signs of precipitated withdrawal were observed only after administration of Ro15-1788. These results indicate a heterogeneity in the effects of benzodiazepine antagonists. Further, these results suggest that, in contrast to some currently accepted notions, the inverse agonist is acting at a site that is distinct from that at which the pure antagonists act, or that the inverse-agonist activity that is obtained in nontolerant subjects is mediated through a nonbenzodiazepine receptor site. Studies of competitive antagonism of the effects of these compounds, particularly an apparent pA_2 analysis of the effects of ethyl-B-carboline-3-carboxylate, will be undertaken to better assess these possibilities.

Project: Reinforcing and Punishing Effects of Benzodiazepine Receptor Ligands and Other Sedative/Hypnotics.
Investigators: J.L. Katz and S.R. Goldberg

Benzodiazepines are among the most widely prescribed drugs. The widespread use of these compounds leads to concerns over their possible abuse. The present studies are designed to provide a characterization of the possible conditions that promote benzodiazepine self-administration. Additionally, behavioral effects of inverse agonists will be investigated. These compounds produce effects that are in many respects opposite those of benzodiazepines. These drugs will be examined as noxious stimuli that may

suppress behavior through a punishment process and as pharmacological treatments that may alter the reinforcing effects of benzodiazepines. Benzodiazepine administration may exacerbate the punishing effects of the inverse agonists through the induction of acute dependence.

In initial studies of the punishing effects of drugs, it was determined that the inverse agonist, ethyl-B-carboline-3-carboxylate, suppressed responding in a specific manner, i.e., suppressed responding only in the component in which injections were scheduled. Subsequent studies have been examining the antagonism of this effect with the relatively pure benzodiazepine antagonist, Ro15-1788. These studies have shown that Ro15-1788 antagonizes the punishing effects of ethyl-B-carboline-3-carboxylate and that the antagonism is dose-related. The functions that have been collected at this point appear to be sufficient for an apparent pA_2 analysis of the effect. This will provide information that will be of use in determining the receptor mechanism by which these drugs are exerting their behavioral effects.

Project: Comparative Studies of Drug Self-Administration in Monkeys and Human Volunteers.
Investigators: J.E. Henningfield, R. Lamb, K. Preston, J.L. Katz, C.W. Schindler, and S.R. Goldberg

One approach to assessing the dependence-producing effects of drugs is to compare the functional characteristics of behavior reinforced by drug injection in different species. In this experiment, a second-order schedule with fixed-ratio (FR) components is being used to compare responding maintained by drug administration in humans to that maintained in monkeys. Under second-order schedules, every time the subject has completed a fixed number of responses (fixed-ratio), he will be presented with a brief stimulus (light/tone) which has been previously associated with an injection of drug; only after a fixed interval of time has passed or a fixed number of fixed-ratio components has been completed will presentation of the brief stimulus actually coincide with injection of drug. The use of second-order schedules in this study permits repeated sequences of behavior with relatively little disruption by the direct effects of drug administration. Since drug is injected only at the end of each session, it is also possible to avoid the use of catheters by utilizing an intramuscular route of administration. Comparisons will be made between doses and schedules, within species and across species. These studies provide an opportunity to evaluate the role of conditioned stimuli in human and non-human drug-seeking behavior. Additionally, all human self-reported subjective effects will be evaluated for dose-dependent discriminations.

One phase of a study on human morphine self-administration has recently been completed. In this study, research volunteers with a history of opioid abuse resided on the Clinical Research Ward of the ARC. Once each weekday, subjects could respond under a fixed-ratio 30 (fixed-ratio 100:S) second-order schedule of intramuscular injection. Subjects were instructed that they could earn an injection by responding on the lever and that conditions may change on a weekly basis. Subjects completed computerized

questionnaires of mood before and after the opportunity to earn drug and computerized questionnaires of drug-effect after the opportunity to earn drug. This study demonstrated that drug self-administration procedures are extremely sensitive measures of the behavioral effects of morphine. Doses of morphine as low as 3.75 mg of morphine sulfate reliably maintained more drug-seeking behavior than did placebo, even in subjects who consistently identified this dose as placebo and denied feeling any drug effect. Ongoing studies are examining the effects of removing the brief stimulus presentations on the self-administration of different doses of morphine.

Project: Drug Effects on Classical Conditioning in Rabbits.
Investigators: C.W. Schindler, S.R. Goldberg, J. Harvey, and S.J. Weiss

The purpose of this project is to investigate the effects of drugs of abuse on classically conditioned responses. The rabbit nictitating membrane response preparation is being used because it allows one to unequivocally attribute the effects of a drug to the associative processes involved with classical conditioning, the sensory processing of the conditioned or unconditioned stimuli, or some combination of these processes. The pharmacological specificity of the effects of opiates are being investigated by studying the effects of opiates purported to be agonists/antagonists at mu, kappa, sigma and delta receptors. These studies have revealed that the mu and kappa opiates have a similar action on classical conditioning, while the sigma opiates appear to act through a different mechanism. The effects of mu and kappa opiates are clearly antagonized by naloxone, while the sigma opiates are not. The delta receptor agonists will be studied using intracerebroventricular (i.c.v.) injection since most of these drugs are peptides which are rapidly degraded when given systemically. Thus far, this technique has been developed using d-ala-leu-enkephalinamide. This drug has a clear effect on acquisition of classically conditioned responses and has a greater potency when injected into the acqueduct of the III ventricle than when injected into the lateral ventricle. This finding is in agreement with anatomical studies which indicate that the locus of this type of learning is confined to the brainstem region.

In order to compare the findings in rabbits to other species, the effects of opiates has also been studied using locomotor activity since locomotor activity has been studied extensively with rats and mice. Again, similarities are found between mu and kappa opiates; both decrease locomotor activity and both are antagonized by naloxone. The sigma opiates also decrease locomotor activity, but this effect is not antagonized by naloxone. Naloxone by itself also decreases locomotor activity at doses below those typically antagonized by mu or kappa opiates.

Project: Cardiovascular Changes Induced by Cocaine in Squirrel Monkeys.
Investigators: G.B. Nahas (terminated 8/31/87), R. Trouve' (terminated 8/31/87), C. Vinyard (terminated 9/11/87), C.W. Schindler, and S.R. Goldberg

Over the past several years, more and more people are using cocaine over prolonged periods and are administering higher and higher doses of the drug. This increase in abuse of cocaine has been paralleled by an increase in

emergency room admissions for cocaine toxicity, most often involving in disruption of cardiovascular function. Despite these reports, there has been relatively little basic research on the effects of acute and chronic cocaine administration on cardiovascular function in non-human primates and, in addition, there has also been little effort directed toward determining the effects of chronic cocaine on behavior in non-human primates. Therefore, the purpose of this project is to investigate the effects of acute cocaine administration on cardiovascular function.

Two experiments have been performed. In the first, three consecutive cocaine injections (0.5, 1.0, and 2.0 mg/kg) were given at 30 minute intervals over the course of a 120 minute session. Each cocaine injection was preceded either by a saline injection or by an injection of a calcium channel antagonist. Injection of 1.0 - 2.0 mg/kg of cocaine led to an increase in blood pressure and a decrease in heart rate. The following EKG anomalies were noted: atrial fibrilation, premature ventricular contractions and ventricular tachycardia. All of these effects were antagonized by the calcium channel antagonists. In the second series of experiments, a single dose of cocaine was administered and its effects were observed over the following 40 min. Higher doses of cocaine (1-3 mg/kg) led to clear increases in blood pressure. Heart rate was also initially decreased in all animals, but was subsequently increased in at least some of the animals.

Section on Behavioral Genetics of the Behavioral Pharmacology and Genetics Laboratory

Overview

This Section conducts behavioral and pharmacogenetic studies using primarily animal models to investigate the contribution of genetic factors to drug abuse, the central mechanisms of drugs of abuse, and the commonality between various drug-related behaviors. This Section also conducts rodent breeding programs to provide the Addiction Research Center with genetically-specified animal populations for use in studies of drug abuse.

The overall present and future goals of this Section are: (1) to determine the extent to which genetic factors mediate substance abuse; (2) to identify specific gene loci related to substance abuse; and (3) to provide the Addiction Research Center (ARC) with a program in genetics to aid the Institute in fulfilling its scientific mission.

The general aims of this section over the next several years are the systematic extension of ongoing research plus the development of new projects and the establishment of a significant pharmacogenetic database regarding operant drug self-administration and sensitivity.

The specific aims are:

To produce a comprehensive genetically and operantly-defined database of drug self-administration data within two commonly utilized rodent

species, namely mice and rats, which the Branch and others can subsequently incorporate into studies examining the biochemical and environmental mediators of drug self-administration.

To produce a similarly defined database of schedule controlled behavior and other acute drug effect data within the same genetically defined strains of rats and mice, so that comparisons can be made between the effects of drugs on operant responding and other phenotypes relevant to acute response to drugs.

To determine, through the use of genetic correlations and other genetic methods, such as Mendelian analysis, diallel analysis and heritability estimates, quantitative estimates of genetic contributions to drug effects as well as the relationship between drug self-administration and other drug-related variables, such as initial sensitivity, to ascertain the degree of common genetic control among these factors.

To establish, through collaborative efforts with other ARC neurochemists, systematic studies concerning the biochemical and genetic substrates of drug effects, particularly drug-seeking behavior.

Where genetic differences in response to a drug have been shown to result from a small number of genes, to coordinate the elucidation of those gene loci and gene products through joint studies between Behavioral Genetics personnel and other ARC molecular biologists.

Summary of Ongoing Research

Project: Genetic Factors in Acute Response to Drugs.
Investigators: S.R. Goldberg and F.R. George

Strain analyses of acute changes in locomotor activation by cocaine have been completed in five rat stocks and seven mouse stocks. In addition to the expected differences in potency and efficacy there are three other novel and significant findings of this work. First, a rat strain (NBR) has been identified which shows an extreme activation response to cocaine, with scores approaching one order of magnitude greater than any other rats tested. Second, a mouse line, the LS/Ibg, has been found to show no cocaine-induced increases in activity, across a wide range of doses. The identification of these outlying genotypes is important since it provides an effective tool for elucidating the biochemical substrates of cocaine's activating effects. Third, it has been found that mice, but not rats, exhibit a low dose decrease in locomotor response to cocaine and that this effect is genotype dependent. Interestingly, the strain distribution pattern (SDP) of this low dose decrease is such that it suggests the possibility of a single or a very low number of genes involved in the mechanism of this effect.

In addition, strain analyses of acute changes in locomotor activation by amphetamine have been completed in four rat strains. These strains exhibit large differences in potency and efficacy in response to acute injections of

amphetamine. Importantly, the SDP of response to amphetamine is different from the SDP of response to cocaine, indicating that the mechanisms of behavioral activation in response to these two stimulants are associated with different neuronal sites.

Moreover, the effects of repeated injections of cocaine on activity have been examined and the results indicate that the degree of sensitization to the stimulant effects of cocaine is independent of the initial cocaine dose. As long as the initial dose of cocaine is above a threshold level, full sensitization occurs, even when exposures to cocaine are several weeks apart. In this study, mice were initially injected with vehicle or one of several doses of cocaine (0 to 76 mg/kg i.p.). After establishing this dose response curve, mice were given repeated injections with a mildly activating dose of cocaine (10 mg/kg) once every three weeks. Each mouse received a total of four injections. All behavioral activating initial doses of cocaine were effective in producing sensitization to the second injection of cocaine. No further increases in response to cocaine were seen at any of the later time points, suggesting that maximum sensitization of cocaine can be produced with a single active dose.

Moreover, the effects of morphine on locomotor activity have been examined in seven mouse genotypes and the results indicate that there are large differences in the behavioral activating and behavioral depressant effects of morphine. In addition, genotypes have been identified which show no behavioral activating response to morphine; these may provide a valuable tool in elucidating the mechanisms of this behavior.

Further, the effects of prenatal treatment with cocaine on fetal mortality, birth weight, and behavioral development have been evaluated. Results obtained to date indicate that prenatal treatment with cocaine (30 mg/kg twice daily) produces dramatic deficits in fetal survivability as well as large decreases in body weight and litter size, as well as decreased developmental progress. In addition, significant genetic differences in these effects were identified. Some strains were severely affected, while others were only mildly affected or not affected at all.

Project: Genetic Factors in the Reinforcing Effects of Drugs.
Investigators: S.R. Goldberg and F.R. George

An important component of the Behavioral Genetics Section relevant to the mission of the ARC is the study of genetic factors in substance abuse using animal models of drug-seeking behavior. Most self-administration studies with non-alcohol drugs have used the intravenous route for administration of the drug. However, because of the large number of animals required for genetic studies, it was important to develop other less invasive and longer lasting models of self-administration. Drawing upon experience with models of ethanol self-administration, procedures have been developed for the oral delivery of cocaine, etonitazine (ETZ), a potent, orally effective opiate agonist, and amphetamine.

These studies have produced the following important findings:

(1) There are large genetic differences in the reinforcing efficacy of ETZ. In particular, Lewis rats show strong levels of responding for ETZ under various conditions, while F344 rats have not shown any consistent patterns of responding for ETZ regardless of the condition or training procedure used. This report will be the first to demonstrate in a systematic, conclusive manner that reinforcement from non-alcohol drugs is mediated significantly by genetic factors.

(2) Cocaine can be established as a positive reinforcer via the oral route. This work utilized previously established ethanol-maintained behavior to implement a cocaine substitution procedure in C57BL/6J mice. Orally delivered cocaine maintained responding under intermittent schedules of reinforcement and responding maintained by cocaine significantly exceeded responding maintained by the vehicle. These results will provide the first report of reinforcement by orally delivered cocaine and may prove valuable in providing an alternative route of cocaine administration as well as a novel species with which to investigate environmental and biological components of cocaine self-administration behavior. The procedures developed during this study are now being used to examine orally delivered cocaine as a reinforcer across several rat strains. Importantly, the same strains are being used in the locomotor activity studies, thus serving as an aid in developing a comprehensive pharmacogenetic database of use to researchers interested in the substrates of substance abuse. These same strains are also being used in a study examining reinforcement from cocaine using the i.v. route. This work will integrate well with existing i.v. data on cocaine self-administration and will also permit comparison with results obtained using the i.v. route with results using the oral route.

(3) Initial studies with orally delivered amphetamine suggest that large genetic differences exist in the reinforcing effects of this drug. Lewis rats appear to respond more for amphetamine than for water, while F344 rats apparently do not change their response rate. It is interesting to note that to date, ethanol, ETZ, cocaine, and possibly amphetamine have been established as positive reinforcers in LEWIS rats and, with the exception of amphetamine because it has not yet been tested, C57BL/6J mice. Conversely, in F344 rats, only ethanol has been shown to function as a reinforcer, and only to a minimal extent. These results address the important question of commonality of drug seeking behavior and demonstrate the utility of pharmacogenetic models in the study of substance abuse.

A third important accomplishment of the Behavioral Genetics Section of Behavioral Pharmacology Genetics Laboratory has been the establishment of a Rodent Breeding Facility within the Institute which is currently providing ARC staff with several hundred genetically defined rats and mice per month. The genotypes are chosen on the basis of their relevance to studies of

substance abuse, (i.e., either they have been studied in other drug research), or are genetically unique with regards to a trait of interest to researchers at the ARC. In addition, initial studies are currently underway which involve genetic crosses of rodent strains known to differ in responses to cocaine in order to determine the mode of transmission of the genes responsible for mediating sensitivity to and reinforcement from cocaine.

An important extension of research in behavioral genetics is conducted in other ARC laboratories. In recent 2-deoxyglucose (2-DG) studies, Dr. London and associates have found that while F344 rats did not show significant changes in brain 2-DG levels upon administration of a 20 mg/kg dose of cocaine, Lewis rats showed significant changes. This correlates well with locomotor activity studies in which Lewis rats exhibited significant increases in locomotor activity at 20 mg/kg but F344 rats did not show increases until they were given 40 mg/kg.

2. Neuropsychopharmacology Laboratory - Steven R. Goldberg, Ph.D., Acting Chief

Overview

This Laboratory conducts studies on the neuroanatomical substrates which mediate the acute and chronic effects of substances of abuse. Studies are conducted to examine neuropharmacological modes of action by which drugs of abuse produce discriminative and reinforcing stimuli as well as changes in physiological parameters, including heart rate, pupil diameter, body temperature and spinal cord reflex activity. Studies are also conducted on the neuroanatomical substrates which mediate the behavioral and physiological effects of drugs of abuse by administering drugs into discrete neuroanatomical sites of the central nervous system and by evaluating the effects of neurochemical lesions on the physiologic and behavioral effects of drugs of abuse.

The Laboratory utilizes operant behavior methodologies, pharmacological strategies, such as comparisons of the effects of selective agonists and antagonists and development of tolerance and cross tolerance to different drugs, and neuroanatomical techniques, such as intracranial self-stimulation. Studies are conducted to define the role of various neurotransmitters and neuropeptides as well as the neural substrates of rewarded behaviors, in particular the self-administration of drugs of abuse. Research is directed toward a more complete understanding of the role of specific brain loci and neurohumors in mediation of the actions of cocaine and other drugs of abuse in producing reinforcing stimuli.

Summary of Ongoing Research

Project: Neural Substrates of Behavior Maintained by Intravenous Psychomotor Stimulant Self-Administration.
Investigators: L.J. Porrino and L.G. Sharpe

Because cocaine has become a more frequently used drug of abuse, the need for determining means of treatment have become more important. In order to develop medications useful for the treatment of cocaine abuse, it is necessary to understand cocaine's actions on specific brain neurotransmitter systems.

In these studies, lever pressing behavior on a fixed ratio schedule was maintained by i.v. psychomotor stimulant injection. It has been found that IVSA (i.v. self-administration) of cocaine can be altered by the administration of the specific dopamine D1 antagonist, SCH-23390. Manipulations of the serotonergic system altered amphetamine self-administration. These results indicate possible differences in the neurochemical substrates of the reinforcing properties of amphetamine and cocaine. The results also show that other psychomotor stimulants, e.g. amfonelic acid, another non-amphetamine class psychomotor stimulant, also has abuse potential in that it too is self-administered. Furthermore, its actions appear to be similar to cocaine in that D1 antagonists, but not serotonergic drugs, alter amfonelic acid IVSA.

Project: Metabolic Mapping of the Brain during Reinforced Behavior.
Investigator: L.J. Porrino

Brain dopamine systems have been shown to be of importance in the initiation and mediation of both motor behavior and reinforced behaviors. Understanding the way dopaminergic circuits function in these behaviors is significant for determining the way these circuits are modified by drugs of abuse. The purpose of this work has been to use the 2-(14C)deoxyglucose method developed by Dr. Louis Sokoloff and his colleagues to map changes in brain metabolism associated with the performances of rewarded behavior and that are associated with an inability to perform motoric behaviors. Work in association with Dr. Louis Sokoloff and Dr. Conan Kornetsky has been examining the metabolic effects of the administration of cocaine to rats lever pressing for delivery of brief trains of electrical stimulation directly to the ventral tegmental area which contains the cell bodies of the dopaminergic mesocorticolimbic system.

The results indicate that cocaine alone (in doses which are self-administered and increase rates of ICSS) increased metabolism in the nucleus accumbens and prefrontal cortex. In contrast, when cocaine was administered to animals which were engaged in self-stimulating increases in energy metabolism were seen in the olfactory tubercle as well as the nucleus accumbens. Cocaine, then, has different metabolic effects in combination with brain stimulation than when administered alone. The metabolic effects of lesions of other dopamine systems are being examined using a neurotoxin-induced animal model of Parkinson's disease.

Project: Neural Substrates of Reinforcement: Psychomotor Stimulants
Investigators: L.J. Porrino

Artificial activation of the brain's reward pathways either by drugs of abuse or by electrical stimulation can aid in the identification of the neurochemical substrates that mediate the reinforcing properties of drugs of abuse such as cocaine and other psychomotor stimulants.

Intracranial self-stimulation (ICSS) is being used to determine the neurochemical basis for the reinforcing effects of psychomotor stimulants. The effects of psychomotor stimulants, alone and in connection with various antagonists, on ICSS to various brain sites is being tested. Findings have confirmed that cocaine decreases the threshold for ICSS to the ventral tegmental area, a brain region implicated in the mediation of reinforced behavior. Further, this effect can be blocked by the administration of the D1 antagonist, SCH-233990, but not by the D2 antagonist, sulpiride. Dose response curves for these drugs' effects on ICSS thresholds are currently being generated. The effects of the psychomotor stimulant, amfonelic acid, on thresholds for ICSS has been tested and, like cocaine, decreases thresholds. This demonstrates this drug's similarity to cocaine.

Project: The Role of Neurokinins in the Morphine Abstinence Syndrome.
Investigators: L.G. Sharpe and J.H. Jaffe

The neurokinins (substance P, neurokinin A and B, Physalaemin, etc.) may play an important role in the opiate abstinence syndrome because morphine inhibits and naloxone increases their release in the morphine-dependent rat. The purpose of this project is to investigate this possibility by giving drugs (before naloxone) to morphine-dependent rats that would either increase or decrease the efficacy of endogenous neurokinins. The results indicate that morphine-dependent rats depleted of substance P (capsaicin treatment as neonates) showed less severe abstinence signs of rhinorrhea, lacrimation and salivation than did the controls. Captopril (0.3 mg/kg i.p.), a drug that increases peripheral levels of substance P, was demonstrated to enhance the secretory signs of abstinence in the morphine-dependent rat. Pretreatment with capsaicin (125 mg/kg) prevented these enhanced withdrawal signs caused by captopril.

The significance of this project is that it may lead to the development of drugs that would aid in the clinical management of opiate detoxification.

Publications for FY 1987

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DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00001-03 BPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Maintenance of Behavior by Drug Injection

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	S.R. Goldberg	Chief, Preclinical Branch	BPL, ARC, NIDA
Others:	J.L. Katz	Research Psychologist	BPL, ARC, NIDA
	C. Schindler	Staff Fellow	BPL, ARC, NIDA
	M. Swedberg	Foreign Fellow	BPL, ARC, NIDA
	J. Prada	Research Psychologist	BPL, ARC, NIDA
	C. Muntaner	Foreign Fellow	PVL, ARC, NIDA
	R. Lamb	Staff Fellow	BDL, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Preclinical Pharmacology Branch

SECTION

Behavioral Pharmacology Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.14	1.84	0.30

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Schedule-controlled performances provide a meaningful way to analyze drug-seeking behavior in the same way as operant behavior maintained by other events such as food or electric shock. In the present project with squirrel monkeys and rhesus monkeys, the rates and patterns of responding maintained by various drugs, including cocaine, nicotine, methohexital, MDMA and MDA, morphine and chlordiazepoxide are being compared using simple fixed-ratio and fixed-interval schedules and complex second-order schedules with brief stimulus presentation in which the role of brief stimuli in maintaining extended sequences can be assessed. The effects of presession treatments with a range of doses of pharmacologic agonists and antagonists, such as caffeine, specific D-1 and D-2 dopamine antagonists, serotonergic reuptake inhibitors, and alpha-adrenergic antagonists, on responding maintained by i.v. psychomotor stimulant injection or food presentation under fixed-interval, fixed-ratio and second-order schedules will be studied. The interactions of naloxone or naltrexone with behavior maintained under extended second-order schedules of morphine self-administration or food presentation will be explored. These experiments with long second-order schedules in which drug is injected only at the end of the session will be extended to study the reinforcing effects of other drugs, including benzodiazepines and barbiturates. Studies of pharmacological and environmental means of weakening established behavior maintained by different drugs will be continued. In a parallel series of studies, the discriminative stimulus effects of nicotine and cocaine are being explored with a focus on the actions of their metabolites and analogs.

Maintenance of Behavior by Drug Injections

Katz, J.L. and Goldberg, S.R.: Second-Order Schedules of Drug Injection. In M. Bozarth (Ed.): Methods of Assessing Reinforcing Properties of Abused Drugs. In press, 1987.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00002-03 BPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Suppression of Behavior by Drug Injections

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.L. Katz	Research Psychologist	BPL, ARC, NIDA
Others:	S.R. Goldberg	Branch Chief	BPL, ARC, NIDA
	J.A. Prada	Research Psychologist	BPL, ARC, NIDA
	K. Takada	Foreign Fellow	BPL, ARC, NIDA
	C. Schindler	Staff Fellow	BPL, ARC, NIDA
	M. Swedberg	Foreign Fellow	BDL, ARC, NIDA

COOPERATING UNITS *(if any)*

Dept. of Psychiatry, Uniformed Services Univ. of the Health Sciences (J.E. Barrett)

LAB/BRANCH

Preclinical Pharmacology Branch

SECTION

Behavioral Pharmacology Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.35	1.35	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Aversive behavioral effects of drugs were assessed by training squirrel monkeys to respond for food reinforcement in the presence of either of two alternately presented visual stimuli. In the presence of the first stimulus, responses also intermittently produced drug injections, whereas responses only produced food presentation in the presence of the second stimulus. Selective suppression of behavior in the presence of the stimulus associated with drug injections is an indication of an aversive effect of the drug.

The aversive effects of drugs may contribute to an understanding of why some drugs are abused and why others are not.

Suppression of Behavior by Drug Injections - Publications FY 1986

Katz, J.L. and Goldberg, S.R.: Effects of H_1-receptor antagonists on responding punished by histamine injection or electric-shock presentation in squirrel monkeys. Psychopharmacology 90: 461-467, 1986.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00003-03 BPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effects of Drugs on Schedule-Controlled Behavior of Experimental Animals

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	S.R. Goldberg	Chief	BPL, ARC, NIDA
Others:	J.L. Katz	Research Psychologist	BPL, ARC, NIDA
	J.A. Prada	Research Psychologist	BPL, ARC, NIDA
	M. Swedberg	Foreign Fellow	BDL, ARC, NIDA
	C. Schindler	Staff Fellow	BDL, ARC, NIDA

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Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.15	1.10	0.05

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

General information on the behavioral pharmacology of a drug in a pertinent species is necessary to evaluate quantitatively how the drug functions as a reinforcer or a punisher as well as to establish a profile of behavioral effects. Multiple schedules of food presentation with both fixed-interval and fixed-ratio components have been most frequently used in this type of study since they generate a wide range of rates and patterns of responding within a session and provide stable, long-term baselines for chronic studies in individual animals. The present project involves the assessment of both the acute and chronic effects of a variety of drugs, under multiple schedules of food presentation in squirrel monkeys, rats, and pigeons. The drugs studied include psychomotor stimulants, such as cocaine, various cocaine analogs, nicotine and caffeine, various narcotic agonists and antagonists, and benzodiazepine agonists and antagonists. Since the behavioral effects of certain drugs depend on the type of event that maintains behavior, the effects of drugs are also studied on comparable performances maintained by either delivery of electric shock or by termination of a stimulus associated with electric shock. These procedures provide stable, long-term sensitive baselines for quantitative assessment of both stimulant and depressant drug effects. The long-term nature of these baselines also makes them ideal for studying tolerance and cross-tolerance development to chronic treatment with various drugs, including cocaine, caffeine, adenosine analogs, and benzodiazepines.

PHS 6040 (Rev. 1/84) GPO 914-918

Effects of Drugs on Schedule-Controlled Behavior of Experimental Animals

Katz, J.L. and Goldberg, S.R.: Effects of ethylketazocine and morphine on schedule-controlled behavior in pigeons and squirrel monkeys. J. Pharmacol. Exp. Ther. 239: 433-441, 1986.

Katz, J.L.: Effects of ethylketazocine and morphine alone and in combination with naloxone on schedule-controlled behavior in pigeons. Psychopharmacology 92: 508-512, 1987.

Katz, J.L. and Goldberg, S.R.: Effects of caffeine alone and in combination with an adenosine analog on schedule-controlled responding in squirrel monkeys. J. Pharmacol. Exp. Ther. 242: 179-187, 1987.

Katz, J.L., Prada, J. and Goldberg, S.R.: Adenosine antagonist effects of xanthine analogs. Pharmacol. Biochem. Behav., In press, 1987.

Garcha, H.S., Goldberg, S.R., Reavill, C., Risner, M.E. and Stolerman, I.P.: Behavioral effects of the optical isomers of nicotine and nornicotine, and of cotinine, in rats. Br. J. Pharmacol. 88: 298P, 1986.

London, E.D., Wilkerson, G., Goldberg, S.R. and Risner, M.E.: Effects of L-cocaine on local cerebral glucose utilization in the rat. Neuroscience Lett. 68: 73-78, 1986.

Katz, J.L., Prada, J. and Goldberg, S.R.: Effects of adenosine analogs alone and in combination with caffeine in the squirrel monkey. Pharmacol. Biochem. Behav., In press, 1987.

Wilkerson, G., Goldberg, S.R., Risner, M.E. and London, E.D.: Differential sensitivity to cocaine in Lewis and Fischer-344 rats as indicated by local cerebral glucose utilization. Neuroscience Abstract, In press, 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA00004-03 BPL

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Comparative Studies of Drug Self-Administration in Squirrel Monkeys and Humans

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	S.R. Goldberg	Chief	BPL, ARC, NIDA
Others:	J.L. Katz	Research Psychologist	BPL, ARC, NIDA
	C. Schindler	Staff Fellow	BPL, ARC, NIDA
	J.E. Henningfield	Chief, BDL	BDL, ARC, NIDA
	R. Lamb	Staff Fellow	BDL, ARC, NIDA
	J. Prada	Research Psychologist	BPL, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH
Preclinical Pharmacology Branch

SECTION
Behavioral Pharmacology Laboratory

INSTITUTE AND LOCATION
Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.53	0.48	0.05

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Self-administration studies permit an assessment of the relative contribution of environmental and pharmacologic factors to the self-administration of drugs and to changes in response to drugs due to tolerance and sensitization. Parallel comparative studies in squirrel monkeys and humans in which subjects are given the opportunity to self-administer comparable doses of cocaine, morphine and nicotine under similar behavioral schedules and experimental conditions provide a means to assess the generality of biological variables influencing drug self-administration. These studies provide an opportunity to evaluate the role of environmental variables and the role of conditioning in human drug-taking behavior and to examine whether those roles differ from the roles of these variables in animal models of drug-taking. These studies have shown that responding is maintained in human subjects in the same manner in which it is maintained in non-human experimental subjects. Additionally, behavior in humans and squirrel monkeys appears to be a function of similar variables. The stimuli that are associated with injections of cocaine develop conditioned reinforcing effects in humans in a manner similar to the manner in which these effects develop in squirrel monkeys. In humans, reinforcing effects of cocaine, morphine and nicotine can be detected at doses that do not occasion subjective reports of drug effects or drug liking. In one study, for example, low doses of morphine reliably maintained rates of responding above placebo and constricted pupil diameter, but did not reliably alter the self-reports of the human subjects. These results indicate that reinforcing effects of drugs can occur without traditional indications of abuse liability.

PHS 6040 (Rev. 1/84) GPO 914-918

Z01 DA 00004-03 BPL

Comparative Studies of Cocaine Self-administration in Squirrel Monkeys and Humans

Publications

Katz, J.L. and Goldberg, S.R.: Second-order schedules of drug injection: Implications for understanding reinforcing effects of drugs. In N.K. Mello (Ed.): Advances in Substance Abuse, In press, 1987.

Henningfield, J.E., Nemeth-Coslett, R.D., Katz, J.L. and Goldberg, S.R.: Intravenous cocaine self-administration by human volunteers: Second-order schedules of reinforcement. NIDA Research Monograph Series No. 76, 1987, pp. 266-273.

Goldberg, S.R. and Stolerman, I.P. (Eds.): Behavioral Analysis of Drug Dependence. New York, Academic Press, 1986.

Henningfield, J.E., Goldberg, S.R. and Jasinski, D.: Abuse liability and dependence potential of nicotine. In W.R. Martin, G.R. Van Loon, E.T. Iwamoto and D.L. Davis (Eds.): Tobacco Smoke and Nicotine: A Neurobiologic Approach. New York, Plenum Press, In press, 1987.

Henningfield, J.E. and Goldberg, S.R.: Pharmacologic determinants of tobacco self-administration by humans. Pharmacol. Biochem. Behav., In press, 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00005-02 BPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Drug Effects on Classical Conditioning in Rabbits

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: S.R. Goldberg	Chief	BPL, ARC, NIDA
Others: C. Schindler	Staff Fellow	BPL, ARC, NIDA

COOPERATING UNITS *(if any)*

Department of Psychology, The University of Iowa, Iowa City, IA (J.A. Harvey, B.G. Scheurs); Department of Psychology, The American University, Washington, D.C. (S.J. Weiss)

LAB/BRANCH

Preclinical Pharmacology Branch

SECTION

Behavioral Pharmacology Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.20	0.20	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Opiates were studied to determine their effects on acquisition of classically conditioned responses. Studies were also carried out on the effects of opiates on locomotor activity in the rabbit and on the behavioral interaction of various conditioned stimuli.

A. Classical conditioning: Recent studies indicate that the opioid peptide d-ala-met-enkephalin-amide retards acquisition in a manner similar to that of the mu and kappa opiates. In agreement with what is known about the anatomical bases of the classically conditioned nictitating membrane response, injections of the peptide into the lateral ventrical are less potent than into the aqueduct of the 3rd ventricle. This work is currently being continued using other peptides and examining their interaction with naloxone.

B. Locomotor activity. Naloxone reduces locomotor activity in the rabbit at doses not normally thought to have agonist activity (1 mg/kg). This effect of naloxone is not antagonized by either morphine or ethylketocyclazocine or low doses of the GABA agonist muscimol (0.1 mg/kg). This line of inquiry will be continued and the potential tolerance of all the compounds studied will be investigated.

C. Stimulus interactions. A number of studies has been completed examining the interaction of stimuli paired with events that function as positive or negative reinforcers. In general, the results indicate that positive reinforcers interact in an excitatory manner, while the combination of a positive reinforcer and negative reinforcer are mutually inhibitory. It is hoped that this work may be extended to include abused drugs as the positive reinforcers.

The significance of this project lies in the findings that opiates can have varying effects depending on the behavior studied and that opiate antagonists may have agonist function independent of the opiate system.

GPO 914-918

Z01 DA 00005-02 BPL

Drug Effects on Classical Conditioning in Rabbits

Publications - FY 1987

Schindler, C.W., Gormezano, I., and Harvey, J.A.: Effects of morphine, ethylketocyclazocine, U-50,488H and naloxone on the acquisition of a classically-conditioned response in the rabbit. J. Pharmacol. Exp. Ther. Submitted.

Schindler, C.W., and Harvey, J.A.: Effects of N-allylnormetazocine and pentazocine on the acquisition of a classically conditioned response in the rabbit. Pharmacol. Biochem. Behav. Submitted.

Harvey, J.A., Winsky, L., Schindler, C.W., McMaster, S.E., and Welch, J.P.: Asymmetric uptake of 14C-2-deoxy-D-glucose in the dorsal cochlear nucleus during Pavlovian conditioning in the rabbit. Brain Res. Submitted.

Weiss, S.J. and Schindler, C.W.: The composite-stimulus analysis and the quantal nature of stimulus control: Response and incentive factors. Psychol. Rec. 37: 177-191, 1987.

Weiss, S.J., and Schindler, C.W.: Integrating control generated by positive and negative reinforcement: Appetitive-aversive interactions. J. Exp. Psychol.: Animal Behav. Processes. Submitted.

Weiss, S.J., Schindler, C.W., and Eason, R.: The integration of habits maintained by food and water reinforcement through stimulus compounding. J. Exp. Anal. Behav. Submitted.

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00006-03 BPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Behavioral Effects of Opioid Agonists, Opioid Mixed Agonist-Antagonists

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.L. Katz	Research Psychologist	BPL, ARC, NIDA
Others:	S.R. Goldberg	Branch Chief	BPL, ARC, NIDA
	C. Schindler	Staff Fellow	BPL, ARC, NIDA
	J. Prada	Research Psychologist	BPL, ARC, NIDA
	R. Lamb	Staff Fellow	BDL, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Preclinical Pharmacology Branch

SECTION

Behavioral Pharmacology Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.13	0.83	0.30

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project is directed at comparing various effects of opioids. The effects that are assessed are the reinforcing, aversive, analgesic and direct behavioral effects. Additionally, the behavior maintained by opioids is compared to behavior maintained by more conventional reinforcing events, such as food presentation, to determine if there are unique aspects to opioids as reinforcers. Reinforcing effects are assessed under second-order schedules of reinforcement, in which each 30th response produces a visual stimulus and the first sequence of 30 responses completed after the lapse of a fixed period of time produces the stimulus and an injection of drug. Under this schedule, a relatively long sequence of responses can be maintained by infrequent injections and the importance of stimuli associated with drug injections can be assessed. The possible aversive effects of these drugs are assessed in studies of punishment or escape/avoidance. The aversive effects of drugs are possibly mediated through different types of opioid receptors, and that possibility is assessed through studies of antagonists. The direct behavioral effects of these drugs are also assessed as well as analgesic effects. The analgesic effectiveness of the drugs are assessed in subjects trained to discriminate the presence or absence of noxious or non-nonxious stimuli. The potencies of the various drugs are ultimately compared under the different procedures to determine if there is a separation of the effects of the drugs as analgesics and as reinforcing agents. Specific analgesic effects are revealed if the drug disrupts the discrimination of noxious stimuli at doses below those that disrupt discriminations of non-noxious stimuli. Additionally, a drug that is relatively impotent as a reinforcer but more potent as an analgesic will have a better therapeutic index.

Z01 DA 00006-03 BPL

Behavioral Effects of Opiod Agonists, Opioid Mixed Agonist-Antagonists

Publications

Katz, J.L. and Goldberg, S.R.: Effects of ethylketazocine and morphine on schedule-controlled behavior in pigeons and squirrel monkeys. J. Pharmacol. Exp. Ther. 239: 433-441, 1986.

Katz, J.L.: Effects of ethylketazocine and morphine alone and in combination with naloxone on schedule-controlled behavior in pigeons. Psychopharmacology 92: 508-512, 1987.

Katz, J.L. and Goldberg, S.R.: Second-Order Schedules of Drug Injection. In M. Bozarth (Ed.): Methods of Assessing Reinforcing Properties of Abused Drugs. In press, 1987.

Katz, J.L. and Goldberg, S.R.: Second-Order Schedules of Drug Injection: Implications for Understanding Reinforcing Effects of Drugs. In N.K. Mello (Ed.): Advances in Substance Abuse. In press, 1987.

S.R. Goldberg and I.P. Stolerman (Eds): Behavioral Analysis of Drug Dependence. New York, Academic Press, 1986.

Katz, J.L. and Goldberg, S.R.: Preclinical assessment of abuse liability of drugs. Agents and Actions, In press, 1987.

Katz, J.L.: Drugs as Reinforcers: Pharmacological and Behavioral Factors. In J.M. Liebman and S.J. Cooper (Eds.): The Neuropharmacological Basis of Reward. Oxford, U.K., Oxford University Press, In press, 1987.

Schindler, C.W., Katz, J.L. and Goldberg, S.R.: The use of second-order schedules to study the influence of environmental stimulus on drug-seeking behavior. NIDA Research Monograph Series, In press, 1987.

Goldberg, S.R., Schindler, C.W. and Katz, J.L.: The influence of environmental stimuli on responding under second-order schedules of morphine self-administration or food presentation. Pharmacologist 29: 201, 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00007-03 BPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Reinforcing and Punishing Effects of Benzodiazepine Receptor Ligands

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.L. Katz	Research Psychologist	BPL, ARC, NIDA
Others:	S.R. Goldberg	Branch Chief	BPL, ARC, NIDA
	J. Prada	Research Psychologist	BPL, ARC, NIDA
	K. Takada	Foreign Fellow	BPL, ARC, NIDA

COOPERATING UNITS *(if any)*

Department of Chemistry, University of Milwaukee at Madison (J.M. Cook)

LAB/BRANCH

Preclinical Pharmacology Branch

SECTION

Behavioral Pharmacology Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.15	0.85	0.30

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Reinforcing effects of sedatives are assessed in squirrel monkeys trained to respond for i.v. injections of methohexital under second-order schedules of reinforcement. Several benzodiazepines as well as barbiturates will be studied under this schedule.

Punishing effects of drugs are determined under fixed-ratio schedules of food presentation in which some responses produce occasional injections of drugs. Alternating components of the schedule in which responses do not produce injections assure a capacity to separate punishing effects from direct pharmacological effects of the drugs. Suppression of responding is established with histamine and subsequently other compounds are substituted for histamine to assess their punishing effects. This procedure is used for assessing potential anxiogenic effects of the inverse agonists.

The anxiolytic effects of benzodiazepines are assessed in squirrel monkeys trained under fixed-ratio schedules of food presentation in which responses occasionally produce electric shock. The actions of benzodiazepine antagonists are also assessed against the agonist actions of benzodiazepines under the punishment procedures, as well as other behavioral procedures in which responses are maintained by food presentation and in which no punishment is involved. Full-dose effect functions are collected so that an apparent pA_2 analysis can be performed. This may provide information that will be of use in determining the receptor mechanism(s) by which these drugs are exerting their behavioral effects.

PHS 6040 (Rev. 1/84)

GPO 914-918

Z01 DA 00007-03 BPL

Reinforcing and Punishing Effects of Benzodiazepines Receptor Ligands

Publications

Woods, J.H., Katz, J.L. and Winger, G.D.: Abuse liability of benzodiazepines. Pharmacol. Rev., In press, 1987.

Takada, K., Hagen, T.J., Cook, J.M., Goldberg, S.R. and Katz, J.L.: Discriminative stimulus effects of intravenous nicotine in squirrel monkeys. Pharmacol. Biochem. Behav., In press, 1987.

Katz, J.L.: Drugs as reinforcers: Pharmacological and Behavioral Factors. In J.M. Liebman and S.J. Cooper (Eds.): The Neuropharmacological Basis of Reward. Oxford, U.K., Oxford University Press, In press, 1987.

Prada, J., Takada, K., Katz, J.L., Goldberg, S.R. and Barrett, J.: Punishment of behavior with buspirone and gepirone in the squirrel monkey. Fed. Proc. 46: 1300, 1987.

Takada, K., Suzuki, B., Katz, J.L., Hagen, T.J. and Cook, J.M.: Behavioral effects of benzodiazepine antagonists in chloradiazepoxide tolerant and non-tolerant rats. Fed. Proc. 46: 1299, 1987.

Katz, J.L., Muntaner, C. and Goldberg, S.R.: Effects of brief stimuli under second-order schedules of cocaine or methohexital injection. Pharmacologist 29: 158, 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00008-03 BPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Behavioral Pharmacology of Non-Opioid Analgesics

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	S.R. Goldberg	Chief, Preclinical Branch	BPL, ARC, NIDA
Others:	M.D. Swedberg	Staff Fellow	BPL, ARC, NIDA
	T.B. Garret	Lab Technician (through 3/87)	BPL, ARC, NIDA
	E.B. Thorndike	Lab Technician (from 4/87)	BPL, ARC, NIDA

COOPERATING UNITS *(if any)*

B. Nickel, Research Associate, Degussa Pharmaceuticals, Frankfurt, FRG

LAB/BRANCH

Behavioral Pharmacology Branch

SECTION

Preclinical Pharmacology

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.70	0.60	0.10

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Rats were trained to discriminate intraperitoneal injections of either flupirtine (10.0 mg/kg) or D-16949 (2.0 mg/kg) from the no-drug condition in a two choice shock avoidance procedure. Avoidance of electric shocks was contingent upon whether the training drug had been injected (flupirtine 10 min., D-16949 30 min.) prior to the session or not. Putative agonists were substituted for the training drug and putative antagonists were administered in combination with the training drug, respectively. Results generated by this procedure allows for conclusions regarding the pharmacological mechanisms of action to be drawn.

Flupirtine: Results indicate alpha-2 adrenergic mechanisms to be of primary importance in mediating the discriminative effects of flupirtine. Opiate mechanisms have been eliminated on the basis of non-substitutability of opioid analgesics and a lack of effect of the opiate antagonist naltrexone. Apart from the alpha-2 adrenergic system, mechanisms yet to be discovered seem to play a role.

D-16949: Tests with opioid analgesics, phencyclidine, d-amphetamine and LSD indicate lack of similarities in discriminative effects. Tests with serotonergic agonists and antagonists indicate that 5-HT_{1B} mechanisms probably are of primary importance for mediating the discriminative effects of D-16949.

Z01 DA 00008-03 BPL

Behavioral Pharmacology of Non-Opioid Analgesics

Publications

Swedberg, M.D.B. and Shannon, H.E.: Discriminative stimulus properties of flupirtine - A novel non-opioid analgesic. Fed. Proc. 46: 547, 1987.

Swedberg, M.D.B., Shannon, H.E. and Goldberg, S.R.: Discriminative stimulus effects of D-16949, a novel, non-opioid analgesic. Pharmacologist 29: 137, 1987.

Swedberg, M.D.B., Shannon, H.E., Nickel, B. and Goldberg, S.R.: Pharmacological mechanisms of action of flupirtine, a novel centrally acting non-opioid analgesic evaluated by its discriminative effects in the rat. J. Pharmacol. Exp. Ther., Submitted.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00009-01 BPL

PERIOD COVERED

January 12, 1987 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cardiovascular Changes Induced by Cocaine in Squirrel Monkeys

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	S.R. Goldberg	Branch Chief	BPL, ARC, NIDA
Others:	G.B. Nahas	Visiting Fellow (through 8/31/87)	BPL, ARC, NIDA
	R. Trouve	Visiting Fellow (through 8/31/87)	BPL, ARC, NIDA
	C. Vinyard	Technician (through 9/11/87)	BPL, ARC, NIDA
	C.W. Schindler	Staff Fellow	BPL, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Preclinical Pharmacology Branch

SECTION

Behavioral Pharmacology Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.15	0.65	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The effects of cocaine are being studied on a number of physiological parameters in the squirrel monkey. Squirrel monkeys are prepared with both venous and arterial catheters prior to the beginning of the experiment. During experimental sessions, each animal is seated in a standard squirrel monkey chair and connected to a blood pressure transducer via the arterial catheter and a venous catheter connected to a syringe outside an acoustical chamber through which drugs can be administered.

To date, two experiments have been performed. In the first, a series of three cocaine injections (0.5, 1.0, and 2.0 mg/kg) were given over the course of a 120 minute session. Each cocaine injection was preceded either by a saline injection or by an injection of a calcium channel antagonist. Cocaine led to an increase in blood pressure and a decrease in heart rate. The following electrocardiogram (EKG) anomalies were noted: atrial fibrillation, premature ventricular contractions and ventricular tachycardia. All of these effects were antagonized by a calcium channel antagonist. In the second series of experiments, a single dose of cocaine was administered and its effects were observed over the following 40 minutes. Higher doses of cocaine (1-3 mg/kg) led to clear increases in blood pressure. Heart rate was also initially decreased in all animals, but was subsequently increased in at least some of the animals.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00001-02 BGL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Genetic Factors in Acute Response to Drug Administration

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	S.R. Goldberg	Branch Chief	BPL, ARC, NIDA
Others:	F.R. George	Staff Fellow	BGL, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Preclinical Pharmacology Branch

SECTION

Behavioral Genetics Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.80	0.55	0.25

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

With the exception of ethanol, genetic factors have not been widely examined with other abused substances, but existing reports do indicate large genetic differences in both acute sensitivity and predisposition to self-administer drugs, particularly narcotics. In the present project with rats and mice, acute behavioral effects of drug administration will be systematically explored. The drugs to be studied include opiate agonists and antagonists, stimulants, particularly cocaine, benzodiazepines, barbiturates, and phencyclidine. Drug effects will be studied using a variety of behavioral tasks, including open field activity, rearing activity, rotational behavior, paw lick, tail flick, sleep time, rotorod stability, and tilt-plane coordination. Simple physiological measures, such as body temperature, blood pressure, heart rate and respiration rate, may also be assessed. For each drug tested, several doses will be examined to obtain dose-response patterns across a wide range of drug effects. Two to four inbred strains of mice and/or rats will be included in all experiments to determine an estimate of the genetic variation for each behavioral or physiological measure. Where appropriate, these measures will be correlated with each other to estimate the commonality among the acute responses studied. In all of these studies, genotype will be incorporated as an independent variable.

Z01 DA 0001-02 BGL

Genetic Factors in Acute Response to Drug Administration

Publications

George, F.R., Ritz, M.C., Elmer, G.I. and Collins, A.C.: Time course of ethanol's effects on brain prostaglandins in LS and SS mice. Life Sci. 39: 1069-1075, 1986.

Suzuki, T., George, F.R. and Meisch, R.A.: Studies on drug dependence: Strain and sex differences in physiological dependence on pentobarbital in rats. Japn. J. Psychopharmacol. 7: 273-274, 1987.

George, F.R.: Prostaglandin involvement in ethanol's mechanism of action. Alcohol and Alcoholism. Supplement 1, 675-678, 1987.

Ritz, M.C. and George, F.R.: Genetic correlations as a tool for determining the relationship between acute neurosensitivity to ethanol and synaptosomal membrane components. Behav. Genet. 16: 634, 1986.

George, F.R., Porrino, L.J., Shannon, H.E. and Goldberg, S.R.: Genetic differences in activation and sterotypic responses to acute and repeated administration of stimulants in Lewis and F344 inbred rats. Behav. Genet. 16: 618, 1986.

Ritz, M.C. and George, F.R.: Synaptosomal membrane characteristics as determinants of neurosensitivity to ethanol. Alcohol and Alcoholism, ISBRA-86 ABSTRACTS: A73, 1986.

George, F.R. and Ritz, M.C.: Genetic correlation as evidence for the prostaglandin hypothesis of ethanol's actions. Alcohol and Alcoholism, ISBRA-86 ABSTRACTS: A71, 1986.

George, F.R., Porrino, L.J. and Goldberg, S.R.: Genetic factors in acute response to cocaine. Fed. Proc., In press, 1987.

George, F.R., Porrino, L.J. and Goldberg, S.R.: Differences in locomotor activation and lethality in response to acute administration of cocaine across several rat genotypes. Behav. Genet., In press, 1987.

George, F.R.: Indomethacin blocks ethanol-induced disruption of fixed ratio responding in rats. Alcoholism. 11: 215, 1987.

George, F.R., Porrino, L.J. and Goldberg, S.R.: Genetic Factors in Behavioral and Lethal Responses to Cocaine in Rats. NIDA Research Monograph Series, Proceedings of the 49th Annual Scientific Meeting, Committee on Problems of Drug Dependence, Inc., In press, 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA00002-02 BGL

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Genetic Factors in Drug Self-Administration

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	S.R. Goldberg	Branch Chief	BPL, ARC, NIDA
Others:	F.R. George	Staff Fellow	BGL, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH
Preclinical Pharmacology Branch

SECTION
Behavioral Genetics Laboratory

INSTITUTE AND LOCATION
Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.80	0.55	0.25

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The objectives of the proposed research are to identify and to examine factors that control drug reinforced behavior using genetically divergent rat and mouse populations. The methodology and principles of operant conditioning and pharmacogenetic analysis will be used. The studies will be limited to conditions in which the drug is taken orally and functions as a positive reinforcer. The focus will be on the variables that control drug reinforced behavior, especially genetic variables, but also including pharmacological variables and environmental variables, e.g., food deprivation/satiation and other dietary factors. Emphasis will be given to systematically studying variables over a range of values and interactions among variables will be parametrically explored. The proposed studies are important because (1) drug intake will be examined under conditions in which it is taken orally and functions as a reinforcer; (2) they will explore genetic and environmental factors and their interactions which contribute to drug self-administration; and (3) they involve the use of genetically defined animals to generate information about the degree to which genetic factors regulate drug-seeking behavior, an approach developed in this Laboratory which may contribute to a systematized body of knowledge that could aid in the analysis of the complex problems of drug abuse.

PHS 6040 (Rev. 1/84) GPO 814-918

Z01 DA 00002-02 BGL

Genetic Factors in Drug Self-Administration

Publications

Elmer, G.I., Meisch, R.A. and George, F.R.: Mouse strain differences in operant self-administration of ethanol. Behav. Genet. 17: 439-451, 1987.

Suzuki, T., George, F.R. and Meisch, R.A.: Differential establishment and maintenance of oral ethanol reinforced behavior in Lewis and Fischer 344 inbred rat strains. J. Pharmacol. Exp. Ther., In press, 1987.

Elmer, G.I., Meisch, R.A. and George, F.R.: Differential concentration-response curves for oral ethanol self-administration in C57BL/6J and BALB/CJ mice. Alcohol 4: 63-68, 1987.

Suzuki, T., George, F.R. and Meisch, R.A.: Lewis and Fischer 344 inbred rats differ in ethanol self-administration. Jpn. J. Psychopharmacol. 7: 105-106, 1987.

Meisch, R.A. and George, F.R.: Influence of genetic factors on drug reinforced behavior in animals. National Institute on Drug Abuse Monograph, In press, 1987.

George, F.R.: Genetic and environmental factors in ethanol self-administration. Pharmacol. Biochem. Behav. 27: 379-384, 1987.

George, F.R.: The use of genetic tools in the study of substance abuse. Alcohol.: Clin. Exp. Res., In press, 1987.

George, F.R. and Khazan, N.: The experimental analysis of drug self-administration. Pharmacol. Biochem. Behav. 27: 365-366, 1987.

George, F.R. and Meisch, R.A.: The Use of Behavior Genetic Methods in the Study of Behavioral Pharmacology. In T. Thompson, P.B. Dews, and J.E. Barrett (Eds.): Advances in Behavioral Pharmacology. New York, Academic Press, In press, 1987.

Elmer, G.I., Meisch, R.A. and George, F.R.: The establishment and maintenance of oral ethanol self-administration in inbred mice. The Pharmacologist 28: 235, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00005-02 NPP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Role of Neurokinins in the Morphine Abstinence Syndrome

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	L.G. Sharpe	Research Psychologist	NPP, ARC, NIDA
Others:	J.H. Jaffe	Director	ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Preclinical Pharmacology Branch

SECTION

Neuropsychopharmacology Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.75	0.5	0.25

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The neurokinins (substance P, neurokinin A and B, Physalaemin, etc.) may play an important role in the opiate abstinence syndrome because morphine inhibits and naloxone increases their release in the morphine dependent rat. The purpose of this project is to investigate this possibility by administering, to morphine-dependent rats (before naloxone), drugs that would be expected to either increase or decrease the efficacy of endogenous neurokinins. The results indicate that morphine-dependent rats depleted of substance P (capsaicin treatment as neonates) demonstrate less severe abstinence signs of rhinorrhea, lacrimation and salivation than did the controls. Captopril (0.3 mg/kg i.p.), a drug that increases peripheral levels of substance P, was found to enhance the secretory signs of abstinence in the morphine-dependent rat. Moreover, pretreatment with capsaicin (125 mg/kg) prevented these enhanced withdrawal signs caused by captopril.

The results from this project may contribute to the development of drugs that could aid in the clinical management of opiate detoxification.

Z01 DA 00005-02 NPP

The Role of Neurokinins in the Morphine Abstinence Syndrome

Publications

Sharpe, L.G. and Jaffe, J.H.: Neonatal capsaicin modifies morphine withdrawal signs in the rat. Neurosci. Lett. 71: 213-218, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA00007-02 NPP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neural Substrates of Behavior Maintained by Intravenous Psychomotor Stimulants

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	L.J. Porrino	Research Psychologist	NPP, ARC, NIDA
Others:	N. Goodman	Pharmacologist	NPP, ARC, NIDA
	L. Sharpe	Research Psychologist	NPP, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Preclinical Pharmacology Branch

SECTION

Neuropsychopharmacology Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.50	0.75	0.75

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Intravenous self-administration (IVSA) is a paradigm that has been used frequently to assess the reinforcing properties of drugs in several animal species. The purpose of the present work is to determine the neuroanatomical and neurochemical basis of IVSA of cocaine and other psychomotor stimulants in the rat. In these studies, lever pressing behavior on a fixed ratio schedule was maintained by i.v. psychomotor stimulant injection. Previous studies in this laboratory have found that IVSA of cocaine can be altered by the administration of the specific dopamine D1 antagonist, SCH-23390. Manipulations of the serotonergic system were without effect on cocaine self-administration, despite clear effects on amphetamine self-administration. These results indicate possible differences in the neurochemical substrates of the reinforcing properties of amphetamine and cocaine. The results also show that other psychomotor stimulants, e.g. amfonelic acid, another non-amphetamine class psychomotor stimulant, also has abuse potential in that it too is self-administered. Furthermore, its actions appear to be similar to cocaine in that D1 antagonists, but not serotonergic drugs alter amfonelic acid IVSA.

The significance of this research involves the importance of characterizing the neurohumors and brain loci involved in rewarded behavior.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00009-02 NPP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neural Substrates of Reinforcement: Psychomotor Stimulants

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	L.J. Porrino	Research Psychologist	NPP, ARC, NIDA
Others:	L.G. Sharpe	Research Psychologist	NPP, ARC, NIDA
	N. Goodman	Pharmacologist	NPP, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Preclinical Pharmacology Branch

SECTION

Neuropsychopharmacology Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.75	0.50	0.25

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to investigate the neuroanatomical and neurochemical substrates that mediate the reinforcing properties of cocaine and other psychomotor stimulants. Intracranial self-stimulation (ICSS) is being used to determine the neurochemical basis for the reinforcing effects of psychomotor stimulants. The effects of psychomotor stimulants, alone and in conjunction with various antagonists, on ICSS of various brain sites are being tested. The results of these studies have confirmed the previous finding indicating that cocaine decreases the threshold for ICSS to the ventral tegmental area, a brain region implicated in the mediation of reinforced behavior. Further, this effect can be blocked by the administration of the D1 antagonist, SCH-23390, but not by the D2 antagonist, sulpiride. Studies are currently ongoing to generate dose response curves for these drugs' effects on ICSS thresholds. The effects of the psychomotor stimulant, amfonelic acid, on thresholds for ICSS have been tested and, like cocaine, this compound decreases thresholds, demonstrating amfonelic acid's similarity to cocaine.

It is hoped that the results of this project will contribute to the identification of neurochemical substrates of the rewarding effects of psychostimulants.

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00010-02 NPP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Metabolic Mapping of the Brain During Reinforced Behavior

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: L.J. Porrino Research Psychologist NPP, ARC, NIDA

COOPERATING UNITS *(if any)*

Laboratory of Cerebral Metabolism, NIMH (L. Sokoloff); Department of Pharmacology, Boston University School of Medicine (C. Kornetsky)

LAB/BRANCH

Preclinical Pharmacology Branch

SECTION

Neuropsychopharmacology Laboratory

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.3	0.3	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The phenomenon of intracranial self-stimulation (ICSS) is considered a productive way of studying reward systems in the brain. The purpose of this research is to identify neural circuits activated during ICSS behavior in rats using the quantitative 2-[14C]deoxyglucose autoradiographic method. Work in association with Dr. Conan Kornetsky and Dr. Louis Sokoloff is examining the metabolic effects of the administration of cocaine on ICSS of the ventral tegmental area, the source of the mesolimbic reward pathway. The results indicate that cocaine alone (in doses which are self-administered and increase rates of ICSS) increased metabolism in the nucleus accumbens and prefrontal cortex. In contrast, when cocaine was administered to self-stimulating animals, increases in energy metabolism were seen in the olfactory tubercle as well as the nucleus accumbens. Thus, it appears that cocaine has metabolic effects in combination with brain stimulation different from those which occur when the compound is administered alone. The metabolic effects of lesions of other dopamine systems are being examined using a neurotoxin-induced animal model of Parkinson's disease.

The results of these studies may contribute to the identification of those brain areas involved in the mediation of reward-motor behavior and to the determination of the way these brain circuits are modified by drugs of abuse.

PHS 6040 (Rev. 1/84) GPO 814-916

Z01 DA 00010-02 NPP

Metabolic Mapping of the Brain During Reinforced Behavior

Publications

Porrino, L.J. and Lucignani, G.: Different patterns of local brain energy metabolism associated with high and low doses of methylphenidate: Relevance to its action in hyperactive children. Biol. Psychiatr. 22: 126-138, 1987.

Porrino, L.J.: Cerebral metabolic changes associated with activation of reward systems. In J. Engel and L. Oreland (Eds.): Brain Reward Systems and Abuse. 1987, pp. 51-60.

Porrino, L.J., Burns, R.S., Crane, A.M., Palombo, E., Kopin, I.J. and Sokoloff, L.: Changes in local cerebral glucose utilization associated with Parkinson's syndrome induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the primate. Life Sci. 40: 1657-1664, 1987.

Porrino, L.J., Burns, R.S., Crane, A.M., Palombo, E., Kopin, I.J. and Sokoloff, L.: Local cerebral metabolic effects of L-dopa therapy in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism in monkeys. Proc. Natl. Acad. Sci., USA, In press.

Palombo, E., Porrino, L.J., Bankiewicz, K.S., Kopin, I.J. and Sokoloff, L.: Comparison of acute and chronic effects of MPTP on local cerebral glucose utilization in monkeys. Proceedings of the International Symposium on Neurotoxicology. New York, Raven Press, In press.

Ho, V.W., Porrino, L.J., Crane, A.M., Kopin, I.J. and Sokoloff, L.: Metabolic mapping of the oculomotor system of MPTP-induced parkinsonian monkeys. Ann. Neurol., In press.

Porrino, L.J.: Using the quantitative 2-(14C)deoxyglucose method for metabolic mapping of the brain during reinforced behavior. In A. Dahlstrom (Ed.) Proceedings of the 6th International Catecholamine Symposium, In press.

Neuroscience Branch

Michael J. Kuhar, Ph.D., Chief

Introduction

The Neuroscience Branch employs a multifaceted research strategy designed to elucidate the mechanisms of action of abused drugs and their effects on biological systems and to develop pharmacological strategies for intervention and treatment. Research areas include molecular genetics, drug receptor binding, cerebral metabolic mapping, electrophysiology, immunology, and positron emission tomography (PET) scanning in humans.

The Branch is organized into two laboratories, the Molecular Pharmacology and the Neuropharmacology Laboratories. These in turn are organized into functional and collaborative units, sometimes with other laboratories.

1. Molecular Pharmacology Laboratory - Chief, Michael J. Kuhar, Ph.D.

Overview

The Molecular Pharmacology Laboratory focuses on the molecular mechanisms of action and molecular effects of drugs of abuse. A strength of the Laboratory involves its research on drug receptors and related neurotransmitter systems. Expertise in the area of molecular genetics is being expanded. In general, a broad, interdisciplinary approach is used in the experimental work conducted in this Laboratory.

A major effort of the Laboratory has been directed at understanding the molecular mechanism of action of cocaine. Specifically, efforts have been successfully directed at identifying the receptor for cocaine which mediates the cocaine effects related to drug abuse and addiction. While several binding sites for cocaine are known, the binding site related to cocaine self-administration has not been specifically identified. Also, while dopamine is known to be involved in reinforcement and reward, and while some have assumed that inhibition of dopamine uptake is the relevant mechanism of action of cocaine, there have been no receptor binding data to support this. Recently, this Laboratory provided such data. The results indicate that the potency of a series of cocaine-like drugs in self-administration studies is correlated with the potency of these same drugs in inhibiting the binding of radiolabeled ligands to the dopamine transporter. Thus, it appears that the receptor related to cocaine dependence and drug self-administration is the cocaine binding site on the dopamine transporter. Because of this demonstrated ability to study the cocaine receptor directly, studies are now in progress examining the receptor in more detail. Aspects of the interaction of cocaine with this receptor will be further studied and an attempt will be made to solubilize the receptor molecule in order to purify and sequence it. These studies also make inroads into experimental work

designed to identify the gene for the receptor and could possibly lead to identification of vulnerability factors in different drug-abusing populations.

While studying drug receptors by in vitro biochemical binding techniques is relatively routine, the ability to study drug receptors in vivo is an emerging frontier. Also, labeling receptors in vivo makes PET scanning studies possible so that these receptors can be studied in living human being by a non-invasive approach. Previously, some pilot data were generated in this Laboratory which indicated that buspirone, a novel anxiolytic, enhances the in vivo labeling of benzodiazepine receptors by a radiolabeled benzodiazpine drug. This raised the question of whether the anxiolytic action of buspirone was somehow mediated through the benzodiazepine receptor. In recent studies, these earlier findings have been confirmed and extended. Moreover, the results indicate that, not only does buspirone enhance in vivo binding, but that a large number of other drugs also enhance the binding. Thus, it appears that this property of receptor binding enhancement in vivo is not unique to buspirone and, therefore, is probably not related to its novel anxiolytic action.

Other in vivo receptor-related studies have been conduted to examine the density of D2 dopamine receptors in schizophrenic patients using PET scanning. Since many schizophrenics exhibit a flat affect and do not experience pleasure (anhedonia), and since dopamine is clearly involved in reward and reinforcement, these studies bear on fundamental problems related to drug addiction. D2 dopamine receptors were found to be elevated in schizophrenics as is suggested by in vitro biochemical studies. These studies may ultimately contribute meaningful insights into how dopaminergic neurons are involved in reward and reinforcement. Moreover, the results of these studies may shed light, not only on addictive processes, but also on other psychiatric diseases.

Stress is a key factor which plays a major role in both the initiation and maintenance of drug abuse. Furthermore, stress produces a profound and sustained change in the body and interacts in a complex manner with psychotropic and addictive drugs. Corticotropin-releasing factor (CRF) is a critical hormone involved with the stress response. In addition to its role in regulating stress responses via the endocrine system, recent evidence suggests that CRF may act as a neurotransmitter in brain and function at least partly as an integrator of the overall stress response in the body. An important ongoing project is to establish CRF as a bona fide neurotransmitter in the CNS. A major effort was directed at studying the receptor for CRF; it has been found that the second messenger system mediating affects of CRF in the CNS involves stimulation of cyclic AMP production. Several other projects include: studies of the action of CRF in the neonatal spinal cord of the rat using electrophysiologic methods; a study of the development of brain receptors for CRF; a detailed study of the CRF-containing olivocerebellar pathway in the brain involving a variety of techniques in several species.

In studies with human tissues, it has been found that CRF-like immunoreactivity is decreased in a variety of neurodegenerative disorders.

These findings suggest that CRF-containing neurons may be targets in certain degenerative disorders and also suggest that a functional role for CRF in the brain may involve cognition, short-term memory and movement.

The goal of another project is to study the mechanisms through which MDMA, MDA, and related amphetamines produce their varied effects. It has been found that MDA and MDMA have relatively high affinities for serotonin uptake sites and serotonin-2 receptors. In addition, these compounds also have fairly high affinities for norepinephrine uptake sites and alpha-2 adrenergic receptors. In vivo studies have revealed that chronic administration of MDA and MDMA causes a selective reduction in both serotonin and its metabolites in discrete brain areas along with drastic reductions in serotonin uptake sites. This latter MDMA-induced neurotoxicity is dependent on both the dose of the drug used as well as the number of times the drug is administered. With respect to neuronal degeneration, one can produce more than a 90% loss of serotonergic nerve terminals in the brain. After 6 months, there is an apparent regeneration of serotonergic nerve terminals (75%). Current studies are focusing on the question of whether or not it is the parent compounds or, perhaps, rather metabolites that are neurotoxic.

There are many other topics of research interest in this Laboratory. Benzodiazepines are drugs of abuse. Steroid drugs are known to affect the CNS and behavior and, accordingly, the effects of steroid hormones have been examined on the benzodiazepine-GABA receptor complex. The results indicate that adrenalectomy alters the so-called GABA ratios, a measure of the coupling between benzodiazepine receptors and GABA receptors. Moreover, these changes were reversed by dexamethasone replacement therapy. Thus, it appears that glucocorticoids can modulate GABA receptor and benzodiazepine receptor functioning and that steroids and adrenal function can affect the action of drugs acting through the GABA receptor complex, such as benzodiazepines.

A number of studies are in the area of molecular genetics. N-methyl-4-phenyl-a,2,3,6-tetrahydropyridine (MPTP), a substance of abuse, is highly neurotoxic in humans, often resulting in Parkinson's disease. A project has been undertaken whose goal is the identification of the genes that are involved in MPTP toxicity. These genes would code for the catecholamine uptake site molecules and other associated molecules. By utilizing a strategy of viral infection-mutation, three distinctive chromosomal regions of PC12 cells have been identified which encode for proteins involved in the drug toxicity. Current efforts are aimed at identifying the DNA sequences of these gene targets which have been cloned and characterized by detailed restriction mapping. Another study is aimed at cloning genetic sequences for an enzyme that degrades substance P. Substance P is a peptide that is involved in withdrawal from chronic morphine as well as the action of other drugs of abuse. The specific enzyme involved is the so-called angiotensin converting enzyme and a relevant gene has been identified and partially sequenced. Computer sequence analysis shows no close homology with other carboxypeptidases. A goal is to isolate and sequence the entire gene for the enzyme.

Pro-opiomelanocortin (POMC) is an important precursor for a variety of hormones including the potent opioid peptide beta-endorphin. The goal of this project is concerned with identifying and isolating various regulatory sequences responsible for POMC expression. Various fragments from the human POMC gene have been subcloned and attached to bacterial genes. Gene transfer techniques show that the POMC promoter sequence alone is insufficient for POMC expression. Another approach was taken to identify the sequence. Nuclear extract from an anterior pituitary cell line protected POMC DNA from digestion with an exonuclease. Nuclear extract from a fibroblast cell line did not protect POMC DNA from exonuclease. This confirms the existence of tissue specific nuclear proteins which recognize and bind to the POMC gene. The protected sequence will be subcloned and analyzed to determine its precise chemical nature.

In AIDS related research, a main effort has been to produce monoclonal antibodies to portions of the human immunodeficiency virus. Very high affinity antibodies are being selected and evaluated for their ability to detect the AIDS viral antigen. Several antibodies to the P24 protein have been produced. One antibody exhibits extremely high immunoreactivity and current efforts are involved in characterizing its affinity and specificity.

Intravenous drug abusers are at higher risk for viral infections such as AIDS. While the disease is propagated through the use of contaminated needles, the potent immunosuppressant effects of a variety of substances of abuse, including opioids, may explain, in part, the increased progression of the disease in drug addicts. Since phencyclidine (PCP) and sigma opioids as well as chronic stress have been demonstrated to cause immunosuppression in vitro, the potential role of sigma opiate drugs and CRF in modulating immune function was examined. Sigma opiate receptors and CRF receptors have been identified in immune tissues. CRF receptors were found in mouse spleen, primarily in splenic macrophages. Also, sigma opiate receptors have been identified in human peripheral blood leukocytes and also in the rat spleen. These results suggest that PCP exerts its immunomodulatory influence via sigma opiate receptors and that endogenous sigma ligands, if in fact they exist, may play a role in immune function.

Summary of Ongoing Research:

A. The Cocaine Receptor Related to Substance Abuse: Kuhar, M.J., Ritz, M., and Sharkey, J.

Having identified, by receptor binding techniques, the cocaine receptor related to substance abuse, efforts are underway to study the receptor in more detail. A priority is to solubilize and purify the receptor. Another goal is to more extensively localize the receptor by autoradiography.

B. Drug Receptors and Addiction: Kuhar, M.J., Ritz, M. and Sharkey, J.

This project is generally directed towards studying the interaction of drugs of abuse with drug and neurotransmitter receptors. A current focus is the interaction of cocaine with the muscarinic cholinergic receptor. Other studies involve investigating the sigma opiate properties of cocaine.

C. Measuring Drug Receptors In Vivo: Kuhar, M.J., Sharkey, J. and Ritz, M.

While measuring and studying receptors in vitro is routine, working with receptors in vivo is currently a frontier. Having identified a relevant cocaine receptor in vitro, efforts are underway to label this receptor in vivo If this were achieved, it may be possible to measure these receptors in vivo in humans using PET scanning.

D. Corticotropin-Releasing Factor (CRF) as a Stress Neurotransmitter in the CNS

CRF is a critical hormone involved with stress responses and recent evidence suggests that CRF is a neurotransmitter in brain. These studies are aimed at characterizing receptor binding sites for CRF at the molecular level and examining the effects of a variety of treatments on these receptors. The projects include:

1) Molecular characterization of CRF receptors in brain using photoaffinity labeling and crosslinking techniques: Grigoriadis, D.E. and DeSouza, E.B.

2) Effects of chronic treatment with antidepressants and benzodiazepines on CRF receptors in CNS: Grigoriadis, D.E. and DeSouza, E.B.

3) Characterization of corticotropin-releasing factor receptors in dissociated brain cell cultures: Kapcala, L.P. and DeSouza, E.B.

4) Effects of acute and chronic stress on CRF receptors in brain and pituitary: Anderson, S., Kant, J. and DeSouza, E.B.

5) Effects of pertussis toxin and cholera toxin on CRF receptors and CRF receptor-mediated adenylate cyclase activity in rat brain: In vitro and in vivo studies: Battaglia, G. and DeSouza, E.B.

6) Localization of CRF receptors in brain and pituitary using fluoresceinated and biotinylated CRF: Tracey, D.E., Boast, C., Rivier, J. and DeSouza, E.B.

E. Role of Corticotropin-Releasing Factor (CRF) and Sigma Drugs in Immune Function

Recent evidence suggests that CRF and sigma receptor agonists such as phencyclidine (PCP) may have immunomodulatory actions. Studies which are currently underway to evaluate the role of these compounds in regulating immune function include:

1) Identification and characterization of sigma receptors in human peripheral blood leukocytes: Wolfe, Jr., S., Kulsakdinun, C., Battaglia, G., Jaffe, J. and DeSouza, E.B.

2) Identification and autoradiographic localization of sigma receptors in rat spleen: Wolfe, Jr., S., Kulsakdinun, C. and DeSouza, E.B.

3) Effects of phencyclidine on natural killer cell activity: In vitro and in vivo studies: Wolfe, Jr., S., Tracey, D.E. and DeSouza, E.B.

4) Corticotropin-releasing factor receptors in mouse spleen: Identification, autoradiographic localization, and regulation by divalent cations and guanine nucleotides: Webster, E.L. and DeSouza, E.B.

5) Corticotropin-releasing factor receptors are present on mouse splenic macrophages: Evidence from biochemical and autoradiographic studies: Webster, E.L. and DeSouza, E.B.

6) Characterization of corticotropin-releasing factor receptor-mediated adenylate cyclase activity in macrophage-enriched populations of mouse spleen: Webster, E.L. and DeSouza, E.B.

7) Effects of endocrine manipulations on CRF receptors in mouse spleen: Webster, E.L. and DeSouza, E.B.

F. The Role of Neurotransmitter Receptors in Human Neuropsychiatric Disorders and Neurodegenerative Diseases

Changes in specific neurotransmitter receptors play a key role in the pathophysiology of various neuropsychiatric disorders and neurodegenerative diseases. These studies are aimed at examining changes in various neurotransmitter receptors including corticotropin-releasing factor (CRF), sigma receptors, PCP receptors and dopamine receptors in human postmortem brain tissue obtained from schizophrenic patients, depressed patients, Alzheimer's disease patients and drug addicts.

1) Changes in CRF-like immunoreactivity and CRF receptors in schizophrenic and depressed patients: DeSouza, E.B., Grigoriadis, D.E. and Cassonova, M.

2) Changes in sigma and PCP receptors in schizophrenic brain: Cassonova, M. and DeSouza, E.B.

3) Sigma receptors in human peripheral blood leukocytes obtained from schizophrenic patients: Effects of PCP on immunosuppression: Wolfe, Jr., S. and DeSouza, E.B.

4) Sigma and PCP receptors in discrete brain areas of patients who overdosed on phencyclidine: DeSouza, E.B. and Cassonova, M.

5) Changes in CRF mRNA in cerebral cortex in Alzheimer's disease: DeSouza, E.B., Thompson, R., Struble, R. and Price, D.L.

G. Neurotoxicity of Selected Drugs to Monoamine Neurons in Brain

Several drugs that are currently used to treat a variety of psychiatric disorders produce their effects through actions on monoaminergic systems in brain. Studies are currently underway to examine the effects of chronic administration of several antidepressant and appetite suppressant drugs that are currently in clinical use, or are being reviewed for approval by the Food and Drug Administration (FDA), for possible neurotoxic action on monoamine neurons in brain.

These include:

1) Fenfluramine preferentially destroys serotonin terminals in rat brain; Quantification of neurodegeneration by measurement of ^{3}H-paroxetine-labeled serotonin uptake sites: Battaglia, G., Zaczek, R., Contrera, J. and DeSouza, E.B.

2) Effects of appetite suppressants on neurotoxicity to monoaminergic neurons in brain: Zaczek, R., Battaglia, G., Contrera, J. and DeSouza, E.B.

H. Neurotoxic Effects of MDA and MDMA (Ecstasy)

The designer drugs, MDA and MDMA, have potent, long-lasting, neurotoxic effects in brain. In addition, MDA, MDMA and related amphetamine derivatives produce a variety of behavioral effects. The goals of the project are to further assess the neurotoxic actions of these drugs and to determine the receptors in brain through which these compounds may produce their neurotoxic actions and behavioral effects. These studies include:

1) In vitro pharmacologic profile of MDMA and MDA at various brain recognition sites: Battaglia, G. and DeSouza, E.B.

2) MDMA and MDA interactions with brain serotonin recognition sites: Evidence for 5-HT_2 receptor agonist activity: Battaglia, G. and DeSouza, E.B.

3) MDMA-induced neurotoxicity to brain monoaminergic neurons visualized by in vitro autoradiography: Differential sensitivity of serotonergic neurons: Battaglia, G., Kuhar, M.J. and DeSouza, E.B.

4) Effects of MDMA treatment on behavioral and neurochemical parameters in primate brain: Insel, T., Battaglia, G., Kuhar, M.J. and DeSouza, E.B.

5) Visualization and quantification of MDMA-induced neurotoxicity in primate brain: Battaglia, G., Insel, T. and DeSouza, E.B.

6) MDMA-induced adaptations in the development of monoamine systems in rat brain as a consequence of drug administration during gestation and neonatal life: Battaglia, G., Zaczek, R. and DeSouza, E.B.

7) Reversed phase high performance liquid chromatography (RP-HPLC) method to detect MDMA, MDA and related amphetamine derivatives in brain and urine: Zaczek, R., Cone, E. and DeSouza, E.B.

8) Identification of MDA and MDMA metabolites in rat brain: Zaczek, R., Battaglia, G. and DeSouza, E.B.

9) Uptake of ^{3}H-MDA and ^{3}MDMA in synaptosomes of rat brain: Zaczek, R., Battaglia, G. and DeSouza, E.B.

I. The Catecholamine Uptake Site

Very little is known about the chemical and molecular nature of this protein, which is presumed to be the cocaine receptor. The catecholamine uptake site also transports the neurotoxin MPTP causing Parkinson's disease in humans. These studies are aimed at identifying and cloning of genes involved in MPTP uptake and neurotoxicity.

1) Retroviral infection in PC12 cells produces MPP+ resistant mutants: Lo, M.M.S., Mamalaki, C., Kadan, M.J. and Dersch, C.M.

2) Phenotype rescue after somatic cell fusion between different MPP+ resistant mutants: Lo, M.M.S., Kadan, M.J. and Mamalaki, C.

3) DNA sequences involved in MPP+ neurotoxicity: Mamalaki, C. and Lo, M.M.S.

4) Membrane proteins are specifically deleted in MPP+ resistant PC12 mutants: Carlson, S.G. and Lo, M.M.S.

J. Structural Gene for the Angiotensin Converting Enzyme

This enzyme degrades substance P and is involved in manifestation of some behavioral signs during withdrawal from chronic morphine addiction. These studies are aimed at identifying and cloning the gene encoding for this enzyme in brain and peripheral tissues.

1) Modification of naloxone-precipitated withdrawal signs by captopril and capsaicin in the morphine-dependent rat: Sharpe, L.G., Jaffe, J.H., Lo, M.M.S. and Porrino, L.J.

2) Characterization of the structural gene for brain and lung angiotensin converting enzyme: Lo, M.M.S. and Mamalaki, C.

K. AIDS Related Research

Efforts are directed at developing monoclonal antibodies to the AIDS viral envelope proteins. Very high affinity antibodies would permit direct detection of virus. Other antibodies directed to conserved antigenic sites may be useful in development of vaccines.

1) Construction of transmissible viral vector encoding for antisense message: Lo, M.M.S.

2) Production of monoclonal antibodies to HIV envelope protein: Lo, M.M.S., Dersch, C.M. and Mamalaki, C.

3) Direct viral detection with very high affinity antibodies to the HIV gp41: Mamalaki, C. and Lo, M.M.S.

L. Human Pro-opioimelanocortin Gene

Regulation of the human pro-opiomelanocortin gene. This gene expresses an opioid peptide. Studies will attempt to identify DNA sequences responsible in its regulation. A specific attempt would be made to identify and clone the regulatory sequences in the human POMC gene. Lo, M.M.S.

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2. Neuropharmacology Laboratory - Chief, Edythe D. London, Ph.D.

Overview

The scientists of the Neuropharmacology Laboratory conduct studies designed to elucidate the neurochemical and electrophysiological mechanisms, as well as the anatomical circuits that mediate the behavioral and physiological effects of abused drugs. Major drugs of interest include opioids, and psychomotor stimulants such as cocaine, methoxyamphetamine derivatives, and nicotine. Studies utilize a wide variety of approaches, including cerebral metabolic mapping in human volunteers and laboratory animals, receptor binding assays, purification and identification of endogenous neuroactive substances, and electrophysiological probes of neuronal circuits and single neurons.

Anatomical systems and physiological mechanisms which mediate euphorigenic and/or analgesic properties of opioids as well as the neuronal pathways and mechanisms associated with opioid tolerance, dependence and withdrawal are subjects of great importance. Within the past year, metabolic mapping studies in human volunteers demonstrated selective decrements in cerebral glucose utilization produced by euphorigenic doses of morphine. These studies allowed the simultaneous measurement of morphine's effects on brain metabolism and on mood and feeling state. Regression analysis revealed a correlation between the reduction in glucose utilization in a specific region of the limbic system (amygdalo-hippocampal) by morphine and functional activity in the temporal pole. This finding suggests that temporal pole activity may have a major influence on the euphoria induced by opioids and perhaps other drugs. Ongoing studies will examine this question in human subjects receiving acute cocaine treatments.

Other studies of opioid effects on cerebral glucose utilization were performed in rats. Both morphine and the mu opioid agonist oxymorphone produced similar effects on cerebral glucose utilization, causing reductions in thalamic nuclei rich in mu receptors and important in somatosensory processing. Nalbuphine, an analgesic with kappa opioid activity, did not produce these effects, but stimulated glucose utilization in kappa receptor-rich areas, including the spinal nuclei of the trigeminal nerve. These areas also were activated by capsaicin which causes the release of substance P, an undecapeptide, from terminals of primary sensory afferents. The results may have implications for the neuroanatomical areas mediating opioid analgesia and capsaicin-induced desensitization. Other studies in which morphine was administered chronically demonstrated complete tolerance to morphine's effects on cerebral metabolism, but marked hypermetabolism during naloxone-precipitated morphine withdrawal. At doses which did not affect cerebral glucose utilization in control animals, clonidine, which ameliorates some of the physiological signs of the opioid abstinence syndrome, antagonized the hypermetabolism induced by morphine withdrawal.

Studies on the isolated spinal cord of the neonatal rat have focused on the role of primary afferent neuropeptides in opioid effects and opioid withdrawal. Recent experiments have provided electrophysiological evidence

that increased release of substance P from primary afferents could contribute to the opioid withdrawal syndrome. Furthermore, evidence from electrophysiological and autoradiographic studies suggested that corticotropin-releasing factor (CRF) is a primary afferent neurotransmitter in the neonatal rat spinal cord.

These investigations have provided valuable insight into the neuroanatomical substrates of acute and chronic opioid administration and advanced the understanding of the physiological actions of acute morphine. These findings are relevant to an understanding of basic functioning of opioid and other neurotransmitter systems as well as to clinical treatment of opioid abuse.

In addition to the aforementioned studies on opioids, the characterization of and the mechanisms of action associated with kappa opioid receptors is being pursued by utilizing receptor binding techniques and in vivo studies. At the molecular level, determining the stability of kappa receptors in animals was a necessary prerequisite before conducting kappa receptor studies in human tissue. Additionally, an evaluation of the interactions of volatile anesthetics and mu and kappa opioid receptor binding sites demonstrated differential effects on the two receptor subpopulations. The results indicated that although volatile anesthetics may have some common membrane effects, the different agents have some unique interactions that vary with the anesthetic and receptor studied.

The observation that naloxone antagonized hibernation suggested the possibility that opioid receptors may be involved in animal hibernation. The involvement of a specific subtype of opioid receptor was evaluated. Results indicate that the kappa receptor may not be involved in inducing hibernation but may be involved in the arousing state of hibernation. Possible involvement of other subtypes of opioid receptors is being evaluated. The well recognized diuretic effect of kappa agonists in rats coupled with the observation that the synthetic pentapeptide BW942C, a recognized mu agonist, produced diuresis in man led to the postulate that BW942C may possess kappa agonist activity. Results suggest that BW942C may represent the first peptide characterized as a partial kappa agonist.

The identification of multiple binding sites for opioids and more recently the subcategorization of these sites have raised questions about the existence of endogenous ligands and defining the relationship between each receptor site and a physiologic response. With respect to the non-opioid, haloperidol-sensitive sigma receptor site, efforts have continued to purify and identify an endogenous ligand. Additionally, several research projects have sought to discover functional effects, which can be attributed to interactions at sigma sites. Local cerebral glucose utilization (LCGU) studies have provided the first evidence that the prototypic ligands at the sigma and PCP receptors, d-N-allylnormetazocine (d-NANM) and PCP, respectively, produce different effects on local cerebral metabolism. Using an in vitro assay approach, electrically stimulated contractions of the isolated guinea pig vas deferens from young adult animals were shown to be potentiated by d-NANM and not by PCP. A cultured cell line (NCB 20) that

expresses sigma receptors is being utilized for electrophysiological studies. Electrical effects altered by sigma agonists and antagonists will be characterized by voltage clamp and patch clamp techniques to identify a specific ion channel as a target of sigma action.

Because of the major concern about cocaine abuse, studies on the distribution and nature of the effects of cocaine and the methoxyamphetamine derivatives (methylenedioxymethamphetamine, MDMA; methylenedioxyamphetamine, MDA) on brain metabolism were performed. Cocaine stimulated cerebral glucose utilization in components of the extrapyramidal motor system, consistent with the view that these brain areas are important to the stereotypies and locomotor stimulation induced by cocaine. Metabolic and behavioral effects varied with the strain of the rat studied, suggesting a genetic variation in cocaine sensitivity. A similar metabolic pattern was produced by MDMA. Ongoing studies focus on cerebral metabolic effects of chronic cocaine administration and cocaine withdrawal.

Studies with nicotine were continued to provide information about the neuronal pathways and mechanisms associated with tolerance, dependence and withdrawal. Nicotine stimulates cerebral glucose utilization in a pattern that closely follows the distribution of receptors for radiolabelled nicotine in vitro. Studies of chronic nicotine effects on LCGU and in vivo mapping of the nicotinic receptor with radiolabelled nicotine have provided important clues about the neuroanatomical substrates of the action of this compound. The studies lay the groundwork for the development of ^{11}C-N-methylnicotine as a probe to study nicotinic receptors in the human brain with positron emission tomography.

A basic study into the drug-receptor interaction at the neuromuscular nicotinic acetylcholine receptor is being concluded this year. New semi-rigid agonists were synthesized, modeled by molecular mechanics and molecular orbital calculations, and tested for their distortion of the receptor's ion channel by patch clamp recording. Subtle changes in agonist structure and electrostatic profile were correlated with large changes in activity.

Another project that was concerned with the neurotransmitter or drug receptors and their relations to postreceptor functional activity was performed using diazepam. In general, diazepam reduced glucose utilization primarily in brain areas rich in benzodiazepine (BZ) type I receptors. Additional studies were performed with CL 218,863, a triazolopyridazine which is a selective agonist at BZ type I receptors. The metabolic pattern produced by CL 218,863 was markedly similar to that produced by diazepam, strengthening the view of a functional heterogeneity of BZ binding sites. It appeared that diazepam, a nonselective ligand in vitro, acts primarily through BZ type I binding sites, calling into question the function of the type II sites.

As drug abusers are at high risk for acquired immunodeficiency syndrome (AIDS), it was of interest to determine if abused drugs, especially those commonly abused by intravenous injection, have an effect on immune function.

If these drugs reduce immunocompetency, the individuals using them would be more susceptible to bacterial and viral infections. Ongoing studies demonstrated a dose-dependent reduction of circulating T-lymphocytes associated with chronic morphine treatment in the mouse, indicating that immunocompetency is compromised by use of this drug. The extension of this study will focus on the specificity of the immunological effect, attempting to identify specific neurohumoral factors or receptors mediating immunosuppressive effects of opioids and other abused drugs.

Summary of Ongoing Research

A. Cerebral Metabolic Studies of Drug-Induced Euphoria: London, E.D. and Broussolle, E.P.M.; Collaborating Investigators: Jaffe, J.H., Herning, R., Pickworth, W., Rippetoe, L.R.; Collaborating Unit: Johns Hopkins Medical Institutions (JHMI) Wong, D.F., Links, J., Dannals, R., Toung, J.K.T., and Wagner, H.N., Jr.; Previous Collaborators: Johnson, R.E., Jasinski, D. and Margolin, R.W. (Vanderbilt University).

Abused drugs produce a positive affective state termed euphoria. The purpose of this project is to delineate those brain areas that are activated or inhibited during drug-induced euphoria. Another objective is the correlation of drug-induced EEG changes with effects on the regional cerebral metabolic rate for glucose (rCMRglu), an index of local brain function. The rCMRglu is measured in human volunteers using [^{18}F]fluorodeoxyglucose (FDG) with positron emission tomography (PET).

Human volunteers with histories of opioid abuse are participating in a double-blind crossover study on the effects of acute morphine. Subjects are tested to determine the reliability and strength of their subjective and EEG responses to two doses of morphine (15 and 30 mg, i.m.) as compared to placebo. Findings in the first 8 subjects show a 8-12% decrease in rCMRglu compared to placebo values in 8 of 22 brain areas studied. Euphoria scores were significantly correlated with rCMRglu in the temporal pole under the morphine condition. Temporal pole rCMRglu was also correlated with the change in rCMRglu in the amygdalo-hippocampal complex. The results indicate a selective effect of morphine on cerebral oxidative metabolism and implicate specific neuronanatomical sites as mediators of opioid euphoria.

A similar protocol has been initiated to map the euphorigenic response to cocaine. A major question to be addressed is the universality of differences in brain areas or circuits involved in euphoria produced by agents from different drug classes.

B. Cerebral Distributions and Mechanisms of Action of Cocaine and 3, 4-Methylenedioxymethamphetamine ("Ecstasy" MDMA): London, E.D., Wilkerson, G., Kimes, A.S., Weissman, A.D., and Johnson, J.E., Collaborating Investigators: Cohen, S.R. and DeSouza, E.B.

The purpose of this project is to delineate the neural effects of cocaine and MDMA and to obtain information about the mechanisms by which these drugs produce psychotropic and possible neurotoxic effects.
The distribution of cocaine's cerebral metabolic effects was studied in the rat using the deoxyglucose technique. Cocaine stimulated LCGU in components of the extrapyramidal motor system and reduced LCGU in the lateral habenula of Fischer-344 rats. A greater sensitivity to cocaine was observed in the LCGU responses of Lewis rats as compared with the Fischer rats. Ongoing studies are directed at identifying whether D_1 or D_2 dopamine receptors are more important to the action of cocaine. In addition, studies with chronic treatment regimens are geared to determine effects of long-term treatment and withdrawal of cocaine.

The effects of cocaine on the fine structure of NG108x15 neuroblastoma cells were also examined. Electron microscopic study of the cells after 3 days of treatment with cocaine revealed an interesting effect of low levels (10^{-9} to 10^{-6} M) of cocaine in the cell nucleus, with implications for altered genetic transmission.

The effects of MDMA on LCGU in the rat also were studied. As with cocaine, rates of LCGU were increased in extrapyramidal motor areas and decreased in the lateral habenula. In addition, an activation of some thalamic nuclei and the visual cortex was observed. The findings were consistent with a psychomotor stimulant action of MDMA, similar to that of cocaine and amphetamine, and with the production of visual hallucinations.

C. Physiological and Metabolic Effects of Acute and Chronic Opioids and Studies of the Opioid Abstinence Syndrome: Fanelli, R.J., Kimes, A.S., Bell, J.A. and London, E.D.; Collaborating Investigators: DeSouza, E.B., Szikszay, M., and Cohen, S.R.

This project is designed to delineate the physiological effects of morphine and the anatomical systems in rat brain and spinal cord that mediate the acute and chronic effects of opioid agonists and antagonists and that contribute to the opioid abstinence syndrome.

The mu agonists, morphine and oxymorphone, decreased glucose utilization in thalamic nuclei, including some of those which have been implicated in somatosensory processing. Nalbuphine, which has kappa agonist and mu antagonist properties, did not produce these effects, but stimulated LCGU in the spinal tract of the trigeminal nerve. These findings suggest that different supraspinal mechanisms mediate the actions of mu versus kappa opioids.

Since substance P has been proposed as a transmitter in nociceptive primary afferent neurons, studies were performed with capsaicin, a peptide which depletes substance P. After subchronic capsaicin treatment, a challenge dose of capsaicin stimulated glucose utilization in dorsal column and brain stem nuclei which receive primary sensory afferent input or are important in autonomic functions. Following subchronic treatment with a greater cumulative dose of capsaicin, a challenge dose did not stimulate glucose utilization in the hindbrain. The findings provide evidence for a central component of the stimulation and subsequent insensitivity observed with continued capsaicin treatment.

Glucose utilization was measured in the brains and spinal cords of rats that were made morphine-dependent by implantation of morphine pellets. No difference in brain glucose utilization (LCGU) was observed. In addition, measures of analgesia were not different in morphine-pelleted rats compared to controls, indicating tolerance. Glucose utilization was also studied in morphine-dependent rats that were treated with naloxone to precipitate withdrawal. Stimulation of glucose utilization was noted in many brain areas, including thalamic structures and the central amygdaloid nucleus. Glucose utilization in the spinal cord was markedly stimulated in the substantia gelatinosa. Clonidine attenuates many signs of opioid abstinence when used clinically. The effect of clonidine was to attenuate some signs of the opioid abstinence syndrome which is associated with a concomitant attenuation of cerebral hypermetabolism during naloxone-precipitated withdrawal.

The individual and combined effects of morphine and diltiazem, a calcium channel inhibitor, on arterial blood gases and pH were assessed in conscious rats. Morphine produced hypercapnia, hypoxia, and slight acidosis. Diltiazem alone did not affect these parameters; however, it delayed the effects of morphine. As an extension of this work, effects of morphine and verapamil, alone and in combination, on arterial blood gases and pH, mean blood pressure and heart rate were assessed in conscious rats. As expected, morphine produced respiratory depression. Verapamil significantly attenuated and delayed the effects of morphine. Morphine caused a slight increase in mean blood pressure; whereas verapamil reduced blood pressure dramatically even in the presence of morphine. Rats treated with morphine showed the most pronounced increase in heart rate, which was antagonized by verapamil. Taken together with previous findings that calcium channel inhibitors facilitate opioid analgesia, the present results suggest that opioids produce analgesia and respiratory depression through different mechanisms.

The effects of morphine on kidney ultrastructure were assessed to obtain information on whether renal degeneration in opioid addicts is due to the opioid per se. Rats were treated chronically with morphine or placebo (s.c. pellets for 7 days). The rats were

sacrificed by aldehyde perfusion, and the kidneys excised, sectioned and prepared for scanning electron microscopy. Morphine-treated rats exhibited significantly altered frequencies of scores for long microprojections, suggesting an increased number of microprojections on glomerular podocytes, and therefore kidney degeneration. Although these effects could have been due to morphine per se, they might have been secondary to the stress of chronic morphine administration.

Electrophysiological and autoradiographic data provided evidence that corticotropin-releasing factor (CRF) is a primary afferent neurotransmitter in the neonatal rat spinal cord and could play a role in opioid withdrawal. CRF depolarizes motor neurons directly and by activating presynaptic neurons. The effect is dose-dependent and is antagonized by a putative CRF antagonist. In addition, CRF greatly enhances the motoneuron depolarizing effects of capsaicin but not glutamate or carbachol, suggesting that CRF may selectively modulate synaptic transmission mediated by slow peptide transmitters.

D. Biological Roles of Sigma and Phencyclidine (PCP) Systems: Biochemical, Neuroanatomical and Electrophysiological Studies: Su, T.-P., London, E.D., Vaupel, D.B., Bell, J.A., and Spivak, C.E.; Collaborating Investigators: Weissman, A.D., Broussolle, E.P.M. and Vu, T.H.; Collaborating Units: JHMI (Hedreen, J.), University of Maryland (Marquis, K., and Moreton, J.E.)

Similarities in the behavioral effects of some arylcyclohexylpiperidine and benzomorphans, typified by PCP and d-N-allylnormetazocine (d-NANM) led to the belief that the actions of such drugs are mediated, at least in part, by the same receptors and/or mechanisms. The purpose of this project is to characterize the receptors, endogenous substances, and anatomical circuits important to the actions of these two classes of compounds. Experiments utilize varied approaches and techniques, including biochemical assay, in vitro preparations, whole animal experiments, and electrophysiology.

An endogenous ligand for sigma receptors, "sigmaphin," has been partially purified from guinea pig brain by molecular sizing and ion-exchange chromatographies. Sigmaphin has been further characterized, and final purification is being conducted.

Studies of sigma and PCP receptors were conducted in neural tissue from a wide variety of species, including humans. The results demonstrated that both sigma and PCP binding sites are phylogenetically old and are distributed throughout the animal kingdom. The affinities of specific ligands for each of the binding sites appeared similar across several vertebrate species. Inhibition studies using [^{3}H]haloperidol as a ligand in the presence

of spiperone (to block labelling of dopamine receptors) in human autopsy brain indicated that the sites labelled are similar to sigma receptors characterized in rodent brain.

The demonstration of sigma receptors in the human brain makes feasible the study of these receptors *in vivo* ultimately by PET. Preliminary studies were conducted in mice to assess the potential utility of radiolabelled d-NANM and haloperidol as ligands for *in vivo* studies of sigma receptors. The results demonstrated a similar pattern of regional sigma receptor binding in the mouse brain using either ligand, in agreement with *in vitro* data in several rodent species. The information obtained could provide the basis for later *in vivo* studies of sigma receptors in humans using positron emission tomography (PET).

The guinea pig vas deferens (GPVD) has been used to develop a bioassay system for sigma and PCP activity. GPVD responded to sigma and PCP-like drugs; whereas, this preparation did not respond to non-sigma drugs such as morphine, D-ala-D-leu-enkephalin and *l*-ketocyclazocine. The study, therefore, provided the first *in vitro* tissue model for sigma receptor activity and demonstrated that sigma binding sites are biologically functional receptors. In this system, sigmaphin had actions similar to those of drugs which interact with the sigma receptor (e.g., *d*-NANM, *d*-pentazocine): (1) sigmaphin potentiated electrically stimulated contractions of the GPVD in a dose responsive manner with a slope parallel to that exhibited by *d*-NANM; (2) sigmaphin-induced potentiation was reversed by putative sigma antagonists (haloperidol, BW234U). It is the continuing effort of this study to discover a tissue preparation which may contain either sigma or PCP receptors.

d-Pentazocine depressed C-reflexes and depolarizing responses to capsaicin in the isolated neonatal rat spinal cord, suggesting sigma receptor modulation in this preparation. Thus, the neonatal rat spinal cord may be another useful bioassay system for sigma activity.

The postreceptor coupling of sigma receptor occupancy to function is unknown. As sigma receptors are expressed on the hybrid neuroblastoma cell line, NCB 20, in near exclusion of PCP receptors, this cell line is being used as a model system to study how sigma receptor activation affects electrophysiological properties of these cells. As the start-up phase of this project approaches successful completion, data on both passive and active properties of this cell line are being accumulated. Any electrical effects altered by sigma-specific drugs will be progressively characterized, by voltage clamp and patch clamp techniques, until a specific ion channel can be identified as a target of (or responder to) the drug.

In vivo assays of sigma and PCP activity were performed in rats using the deoxyglucose procedure. Whereas PCP generally and profoundly

stimulated LCGU in many areas, the effects of the sigma-preferring ligands d-NANM and di-tolylguanidine (DTG) on LCGU were inhibitory. Some brain areas showed decrements in LCGU following PCP treatment, but only after high doses. In some cases d-NANM, which reportedly has more PCP-like activity than DTG, showed a metabolic picture intermediate between PCP and DTG. The results suggest that sigma receptors and PCP receptors are functionally distinguishable by metabolic mapping techniques. Careful dose-response studies are being carried out to delineate the full range of effects of several putative sigma agonists and antagonists.

The abuse potential in humans and the self-administration of PCP by rats has suggested that PCP may affect reward systems. Effects of PCP on LCGU are being studied in rats trained to self-administer PCP on a fixed-ratio schedule. Preliminary observations indicate that the self-administering animals show patterns of LCGU which are similar to naive rats receiving PCP acutely, but at a higher dose. Potential tolerance to the metabolic effects of PCP is being investigated.

Antagonists at sigma receptors may represent a new therapeutic lead to the discovery of potential antipsychotic agents. The sigma antagonists may not elicit undesired extrapyramidal side effects such as those produced by dopamine D_2 antagonists. It was shown that HR 375, a drug which in preclinical trials displayed no propensity to elicit extrapyramidal side effects, was actually a potent sigma ligand, indicating that the potential antipsychotic properties of HR 375 may be attributed, at least in part, to its interaction with the sigma receptors.

E. Studies of Nicotine Receptors and Their Involvement in the Behavioral and Metabolic Effects of Nicotine: Fanelli, R.J., Broussolle, E.P.M., and London, E.D.; Collaborating Investigators: Jaffe, J.H. and Henningfield, J.E.

Goals of this project include elucidating cerebral mechanisms involved in the behavioral effects of chronic nicotine and providing additional information about nicotinic cholinergic receptors. ^{3}H-l-nicotine ([^{3}H]N) was injected i.v. in mice and brains were dissected for measurement of radioactivity. Nonspecific binding was determined by pretreatment with unlabelled l-nicotine. There was a rapid entry of [^{3}H]N into the brain and a decline after 7.5 min. Specific binding was maximum at 5 minutes and fell nearly to zero by 30 minutes. This binding was heterogeneously distributed with labelling highest (45 - 50% of total radioactivity) in the medial and posterior cortex, midbrain, thalamus/hypothalamus and medulla/pons; intermediate (35 - 44%) in the cerebellum, caudate-putamen, frontal and frontoparietal cortex; and lowest (31 - 34%) in the hippocampus and olfactory bulb. Autoradiographic studies

confirmed this distribution. An examination of the specificity of [^{3}H]N binding indicated that all nicotinic agonists tested significantly inhibited binding, while several nicotinic antagonists were inactive.

Following chronic administration of nicotine, an examination of the resulting effects on local rates of glucose utilization in the brain and correlated effects on receptor dynamics and maze performance would be a critical addition to the understanding of the neurochemical and anatomical bases for chronic nicotine effects on behavior. Animals were treated chronically (twice daily for 10 days) with nicotine and glucose utilization was measured. While behavioral tolerance to this treatment was not clearly indicated, several brain regions, including the anteroventral thalamus and substantia nigral pars compacta, showed evidence of tolerance. Other brain regions showed metabolic effects that may be related to withdrawal and receptor upregulation. The analysis of receptor densities and affinities and behavior is currently underway.

F. Cerebral Metabolic Studies of Anxiolytics: Broussolle, E.P.M., Dam, M., and London, E.D.

Effects of diazepam on LCGU were examined to delineate areas that mediate the various effects of the drug (anxiolytic, sedative, etc.). Diazepam selectively reduced LCGU in approximately half of the brain regions examined. The most prominent reductions were obtained in brain areas rich in benzodiazepine type I receptors, defined by in vitro studies with the triazolopyridazine, CL218,872. Additional studies with CL 218,872 produced a metabolic pattern of effects similar to that obtained with diazepam. The results suggested that benzodiazepine receptor subtypes are functionally distinct and that the therapeutic effects of diazepam are mediated by type I receptors.

G. Factors Which Influence Rates of Local Cerebral Glucose Utilization (LCGU): London, E.D.; Collaborating Investigators: Cohen, S.R. and Walovitch, R.; Collaborating Unit: University of Maryland (Selmanoff, M., Wise, P.M., Cohen-Becker, I.R., and Weiland, N.G.)

Regional or local cerebral glucose utilization (rCMRglu and LCGU, respectively) are used extensively as indices of brain function. Therefore, it is important to consider the potential influences of various physiological and psychological factors on cerebral glucose utilization in interpretations of psychoactive drug effects on brain metabolism. Studies of the effects of various conditions on LCGU have been initiated in the rat. Factors considered to date include age, endocrine status, circadian periodicity, restraint stress, and pain.

In studies of the effects of exogenous ovine prolactin, restraint stress and several pain models on LCGU, hyperprolactinemia was

associated with decreased LCGU in the medial forebrain bundle and the dorsal hippocampus. Free-ranging rats had significantly higher rates of LCGU than restrained rats in several areas including the medial septal nucleus, rostral striatum, frontoparietal cortex, and median eminence. The results indicate that prolactin administration may produce inhibition of brain areas that project to the median eminence, where prolactin stimulates dopamine turnover, and that restraint is a factor which could influence LCGU. Neither the formalin nor the tail immersion models of pain produced statistically significant alteration in LCGU.

Studies in young and old ovariectomized rats demonstrated a diurnal rhythmicity in LCGU of the suprachiasmatic nucleus and pineal gland in young and old animals. Although there was no age difference in LCGU of the pineal gland, LCGU in senescent rats was lower than in young rats during both light and dark phases in all hypothalamic areas examined except the suprachiasmatic preoptic nucleus and the median eminence. Middle aged rats primed with estradiol showed an irregularity in the circadian periodicity of LCGU in the suprachiasmatic nucleus, associated with a loss of cyclic reproductive function.

H. Effects of Chronic Drug Abuse on Lymphoid and Brain Receptors: Kimes, A.S., and London, E.D.; Collaborating Units: JHMI (Smith, W.J.)

Studies in mice demonstrate that chronic morphine treatment is immunosuppressive. Chronic morphine treatment reduced spleen/body weight ratios, white blood cell count, lymphocyte counts, total numbers of T-lymphocytes and each of the subclasses of T-lymphocytes distinguishable by monoclonal antibodies (helpers and cytotoxic/suppressors). Effects are dose-dependent, and not blocked by *in vivo* naltrexone. However, chronic morphine treatment failed to change the proliferative response of isolated mouse splenocytes to mitogens specific for T- or B-lymphocytes. Current investigations focus on specificity of the effect to drugs interacting with opioid receptor subtypes (mu, kappa, and sigma), and correlation with effects of chronic morphine treatment on receptors for neuroactive substances in spleen. The binding characteristics of the first of these receptors, the sigma receptor, have been determined and the effect of chronic morphine is being studied presently. Preliminary data indicate that chronic morphine may increase the receptor density of these receptors in splenocytes. Future studies will address the mechanisms by which the immunosuppression occurs and time course of the onset and potential tolerance to the immunosuppressive effect.

I. **In vivo and in vitro studies of kappa receptors: Su, T.-P., London, E.D., and Vaupel, D.B.; Collaborating Investigators: Ori, C.; Collaborating Units: University of Kentucky (Oeltgen, P.R.) and Wheaton College (Bruce, D.S.)**

Subscapularly implanted osmotic minipumps containing naloxone antagonized hibernation of summer active ground squirrels induced by a hibernation induction trigger (HIT) isolated from winter hibernating woodchucks. The possibility of involvement of multiple types of opioid receptors in the HIT-induced hibernation was examined. A kappa opioid receptor selective agonist, U69593, was used to investigate the involvement of kappa opioid receptors in this behavior. Direct infusion of U69593 via osmotic minipumps did not induce hibernation in summer active animals. The infusion of U69593, however, antagonized HIT-induced hibernation. The results suggest, therefore, that HIT may induce hibernation through other types of opioid receptors such as mu and sigma, the effects of which could be reversed by naloxone, and may not involve kappa opioid receptors. Since the kappa ligand U69593 antagonized hibernation, it is tempting to speculate that kappa receptors may be involved in the arousal state of animal hibernation.

In order to examine the possible involvement of kappa opioid receptors in different psychopathological states in humans, the biochemical stability of kappa receptors in storage conditions similar to human autopsy became an essential piece of information. The study was conducted using guinea pig brains. Kappa opioid receptors from the guinea pig brains stored in the same conditions as human autopsy samples are stable for up to 16 hours. The extraordinary stability of kappa opioid receptors will help facilitate our understanding of its possible psychopathological roles.

One of the possible mechanisms of actions of volatile anesthetics is the alteration of neurotransmitter binding to its receptors. Effects of anesthetics, such as N_2O and halothane, on opioid receptors (mu and kappa) were examined. N_2O increased the Kd values for both mu and kappa opioid receptors, but decreased Bmax of kappa binding. Halothane, on the other hand, increased Kd for mu receptors but decreased Kd for kappa receptors with a concomitant decrease in Bmax. Therefore, anesthetics do affect, at least, mu and kappa opioid receptors, both involved in pain perception.

The diuretic effects of the synthetic opioid pentapeptide, BW942C, were evaluated in humans, rats, mice and squirrel monkeys to test the hypothesis that the diuresis is a result of kappa opioid activity. BW942C was shown to bind to mu, kappa and sigma receptors, exhibiting high affinity for mu and sigma receptors, moderate affinity for kappa receptors and no affinity for sigma receptors. In urination studies, BW942C increased urine output at low doses, but decreased urine output at higher doses. The antidiuretic effect of this drug,

like that of morphine, was antagonized by low doses of naltrexone. The modest diuresis produced by low doses of BW942C and the marked diuresis produced by the kappa agonist, U50488, were antagonized by high doses of naltrexone. Thus, results of this study suggest that BW942C may be the first synthetic peptide with affinity for kappa opioid receptors and may be a partial kappa agonist in addition to being a mu agonist. This study raises some interesting questions about the structural requirements for activity at kappa opioid receptors.

J. **Structures and Activities of Semirigid Nicotinic Agonists: Spivak, C.E.; Collaborating Units: NIDDK, NIH (Waters, J.A.), New Jersey Institute of Technology (Gund, T.M.), Univ. Miami (Magleby, K.), Med. College of Georgia (Aronstam, R.), Inst. Psychiatry, De Crespigny Park, London (Stolerman, I.)**

This project aims at understanding one of the most fundamental problems in neurobiology and pharmacology, molecular recognition. It employs the nicotinic acetylcholine receptor, which is the best understood receptor for neurotransmitters. New agonists, synthesized in this laboratory and by Dr. J. Waters, include ring structures to enforce a semirigid shape. Further, refinements in learning the agonists' conformations and electrostatic energy profiles are calculated.

The most useful series of compounds, the isoarecolone methiodide series, consists of eighteen new agonists tested at the frog neuromuscular junction. Although the eponymous, prototype agonist is among the most potent known, 50 times as potent as carbamylcholine, analogues of this series exhibit potencies that range down to only 1/25,000 of this activity despite minor structural modifications.

The receptor reacts to agonists by directly opening a cation channel. The "patch clamp" technique permits one to record the few picoamps of current that traverse this channel; the durations of open and closed channels yield kinetic information on the linkage between the drug and the ion channel. Patch clamp experiments were concluded on the two most potent drugs of the series, isoarecolone methiodide and dihydroisoarecolone methiodide. Although still incomplete, analysis of the data is yielding unexpected findings, including: 1) the existence of a third, previously unknown, open state of the junctional ion channel, and 2) that the kinetics of activation of the ion channel induced by these two drugs is so similar that their 5-fold difference in potency must be due, by exclusion, to differences in rates at which they desensitize the receptor.

Behavioral and binding experiments with isoarecolone and its methiodide were performed using rats. Binding studies of all the agonists of the isoarecolone methiodide series were done using electric organ from Torpedo as a source of nicotinic receptors and

rat forebrain as a source of muscarinic (M1) receptors.

K. **Assessment of the Abuse Liability of PCP-like Compounds: Vaupel, D.B., Shannon, H.E. and Risner, M.E.**

The comparison of the d- and l- enantiomers of N-allylnormetazocine (NANM) and racemic NANM to PCP was conducted to provide a more thorough pharmacologic evaluation of the PCP-like actions of the NANM enantiomers in the dog and to complement previous studies evaluating the pharmacologies of eight PCP analogs and racemic NANM in the dog. The conclusion that d-NANM is more similar to PCP in its pharmacology than l-NANM was based upon data encompassing physiological and behavioral responses as well as operant behavior effects in the dog. The publication of these results during the past year represents the completion of this project.

L. **Investigations of Kappa and Sigma Properties of Antinociceptive Drugs in the Dog: Vaupel, D.B. and Cone, E.**

The rationale for comparing the enantiomers of ketocyclazocine was to identify and selectively antagonize the spinal dog model correlates of kappa and sigma effects based on the hypothesis that kappa effects would be associated with the l-enantiomer and sigma effects with the d-enantiomer. Evaluation of pharmacologic responses, plasma levels, and antagonism data has demonstrated that neither isomer elicits sigma-type activity and l-ketocyclazocine possesses all the kappa activity observed in the dog.

The evaluation of the role of opioid mechanisms in the antinociceptive properties of novel analgesic show that flupirtine-induced antinociception in the dog is primarily mediated by non-opioid supraspinal mechanisms.

Analysis of various dose ratios based upon human abuse data of the antihistamine tripelennamine and the opiate agonist-antagonist pentazocine revealed a complex pattern in the dog with the interaction dependent upon the specific parameter measured.

All experimentation on these projects using dogs has been completed.

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Vaupel, D.B. and Su, T.-P.: A potential bioassay for identifying and classifying PCP and sigma ligands. Pharmacologist 29: 161, 1987.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA00100-02 MPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neurotransmitter Receptors in the Pituitary Gland

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: E.B. DeSouza Chief, Neuropeptide Unit MPL, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Molecular Pharmacology Laboratory, Neuroscience Branch

SECTION

Neuropeptide Unit

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.8	0.6	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Serotonin, catecholamines, and corticotropin-releasing factor (CRF) have been shown to play a major role in regulating pituitary hormone secretion, both through effects in brain and direct actions on the pituitary. The goals of the project were to identify, characterize and localize, using in vitro autoradiography, the relative distribution of serotonin-2, dopamine-2, beta-2 adrenergic, alpha-1 adrenergic and CRF receptors in the rat pituitary gland. In order to define the role of adrenomedullary catecholamines and glucocorticoids in regulating pituitary function, the effects of adrenalectomy were examined on beta-2 adrenergic and CRF receptors in the rat pituitary gland. The identification of the various receptors described above provides further evidence of the importance of these neurotransmitters in regulating pituitary function and demonstrates conditions in which these receptors can be modulated.

PHS 6040 (Rev. 1/84) GPO 914-918

Z01 DA 00100-02 MPL

Neurotransmitter Receptors in the Pituitary Gland

Publications

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00101-02 MPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Role of Corticotropin-Releasing Factor and Sigma Drugs in Immune Function

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	E.B. DeSouza	Chief, Neuropeptide Unit	MPL, ARC, NIDA
Others:	E.B. Webster	Graduate Student	MPL, ARC, NIDA
	S.E. Wolfe, Jr.	Staff Fellow	MPL, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Molecular Pharmacology, Neuroscience Branch

SECTION

Neuropeptide Unit

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.8	0.5	1.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Recent evidence suggests that corticotropin releasing factor (CRF) and sigma agonists such as phencyclidine (PCP) may have immunomodulatory actions. To evaluate the role of these compounds in regulating immune function, studies have been carried out to identify and localize receptor binding sites in rat and mouse spleen and in human peripheral blood leukocytes (HPBL). With regard to CRF, specific high affinity receptors have been identified and characterized in mouse spleen with characteristics similar to those in brain and pituitary. ^{125}I-CRF binding to mouse spleen was found to be linear with increasing protein concentration, saturable and of a high affinity. In autoradiographic localization studies, CRF binding was localized in red pulp regions of the spleen and a high density of CRF binding sites was observed in macrophages; there was a notable absence of CRF binding in lymphoctyes. The preliminary evidence suggests that CRF receptors are primarily located on splenic macrophages. Sigma receptors were identified and characterized in HPBL and rat spleen; the binding sites had kinetic and pharmacological characteristics similar to those for sigma receptors in brain. The highest density of sigma receptors was found in rat spleen with lower but comparable concentrations in HPBL and rat cerebellum. In autoradiographic studies, the sigma receptors appear to be localized primarily to lymphocytes. In preliminary immunological studies, the immunosuppressant effects of PCP on natural killer cell activity have been identified. The data demonstrating the presence of CRF and sigma receptors in immune tissue may indicate a physiological role for these endogenous neurotransmitters in modulating immune function. Sigma drugs could conceivably alter the release of lymphokines and monokines and provide additional mechanisms for the central action of these drugs. Also, the receptors in HPBL leukocytes may represent useful peripheral markers in humans for assessing the role of these receptors in brain.

Z01 DA 00101-02 MPL

Role of Corticotropin-Releasing Factor and Sigma Drugs in Immune Function

Publications

Webster, E.L. and DeSouza, E.B.: Corticotropin-releasing factor receptors in mouse spleen: Identification, autoradiographic localization and regulation by divalent cations and guanine nucleotides. Endocrinology In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00102-02 MPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neurotoxic Effects of MDA and MDMA (Ecstasy)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	E.B. DeSouza	Chief, Neuropeptide Unit	MPL, ARC, NIDA
Others:	G. Battaglia	Staff Fellow	MPL, ARC, NIDA
	M.J. Kuhar	Chief, Neuroscience Branch	MPL, ARC, NIDA
	S.Y. Yeh	Scientist	MPL, ARC, NIDA
	M. Molliver	Assistant Professor, JHU	
	E. O'Hearn	Assistant Professor, JHU	

COOPERATING UNITS *(if any)*

Department of Neuroscience, JHUMI

LAB/BRANCH

Laboratory of Molecular Pharmacology, Neuroscience Branch

SECTION

Neuropeptide Unit

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.3	2.2	0.8

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The goals of the project are: (1) to study the neurochemical mechanisms through which 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA) and related amphetamine derivatives produce their neurotoxic effects in the central nervous system and, (2) to examine the pharmacologic profile of MDA and MDMA at various brain recognition sites.

1. Neurotoxicity: The effects of chronic in vivo administration of MDA and MDMA on brain monoaminergic systems have been examined. These studies included measurements of the content of a variety of brain monamines and their respective metabolites, visualization of brain monoaminergic neurons using immunocytochemistry and in vitro autoradiography. It was found that chronic administration of MDA and MDMA produces selective decreases in both serotonin (5-hydroxytryptamine, 5-HT) and 5-hydroxyindoleacetic acid (5-HIAA), with no major changes in the catecholamines in discrete areas of rat brain. Drastic reductions in 5-HT uptake sites and massive destruction of 5-HT preterminals were found. Following an initial 90% loss of 5-HT uptake sites, the recovery of sites (i.e. neuronal regeneration) occurred over a protracted period of time; a 25% reduction was seen at 6 months after treatment with MDMA. In addition, the immunocytochemical data suggest that it is not the parent compound but rather a metabolite(s) that may be neurotoxic. The autoradiographic data demonstrate that the neurotoxic effects of these compounds on destruction of serotonin terminals is not diffuse but rather is limited to certain brain areas. The neurotoxic effects of MDA and MDMA in rats can be prevented by pretreatment with a serotonin uptake blocker, citalopram.

Neurotoxic Effects of MDA and MDMA (Ecstasy)

2. The pharmacologic profile of MDA, MDMA and their amphetamine derivatives at various brain receptors were examined using in vitro radioligand binding procedures. MDA and MDMA have relatively high affinities for 5-HT uptake sites, 5-HT_{1A} receptors, 5-HT_2 receptors, and sigma receptors; these compounds have moderate to weak affinities for a variety of other brain recognition sites, including pre- and postsynaptic recognition sites for catecholamines, acetylcholine, opioids and various neuropeptides.

Publications

Battaglia, G., Yeh, S.Y., O'Hearn, E., Molliver, M.E., Kuhar, M.J. and DeSouza, E.B.: 3,4-Methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxyamphetamine (MDA) preferentially destroy serotonin terminals in rat brain: Quantification of neurodegeneration by measurement of ^{3}H-paroxetine-labeled serotonin uptake sites. J. Pharmacol. Exp. Ther., In press.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00103-02 MPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Corticotropin-Releasing Factor (CRF) in Human Neurodegenerative Diseases

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	E.B. DeSouza	Chief, Neuropeptide Unit	MPL, ARC, NIDA
Others:	D. Price	Assistant Professor	JHU
	P.J. Whitehouse	Assistant Professor	JHU
	R. Powers		JHU
	L. Walker		JHU
	W.W. Vale		Salk Institute

COOPERATING UNITS *(if any)*

Neuropathology Laboratory, JHU; Clayton Foundation Laboratories for Peptide Biology, The Salk Institute, San Diego, CA

LAB/BRANCH

Molecular Pharmacology Laboratory, Neuroscience Branch

SECTION

Neuropeptide Unit

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The goal of this project is to study the role of brain CRF in neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease and progressive supranuclear palsy. Initially, brain tissue from control and Alzheimer's patients was examined for pre- and post-synaptic markers for CRF. In Alzheimer's samples, the concentrations of CRF-like immunoreactivity were reduced and there were reciprocal increases in CRF receptor binding in affected cerebral cortical areas. These changes were significantly correlated with decrements in choline acetyltransferase activity. Decreases in CRF-like immunoreactivity similar to those described for Alzheimer's disease were also seen in patients who died of Parkinson's disease and progressive supranuclear palsy. In contrast, patients who died of Huntington's disease did not show decrements in CRF-like immunoreactivity in the cerebral cortex but did show significant decreases in CRF-like immunoreactivity in the caudate/putamen. More recently, abnormalities in CRF-like immunoreactive neurons have been demonstrated in patients who died of Alzheimer's disease, that is, the CRF-like immunoreactivity was localized to senile plaques. These results strongly support a neurotransmitter role for CRF in brain and demonstrate, for the first time, a modulation of central nervous system (CNS) CRF receptors associated with altered CRF content. These observations further suggest a possible role of CRF in the pathophysiology of various neurodegenerative disorders. Future therapies directed at increasing CRF levels in brain may prove useful for the treatment of Alzheimer's disease and other neurodegenerative disorders.

Corticotropin-Releasing Factor (CRF) in Human Neurodegenerative Diseases

Publications

Whitehouse, P.J., Vale, W.W., Zweig, R.M., Price, D.L. and DeSouza, E.B.: Reductions in corticotropin-releasing factor-like immunoreactivity in cerebral cortex and Alzheimer's disease, Parkinson's disease and progressive supranuclear palsy. Neurology 37: 905-909, 1987.

Powers, R.E., Walker, L.C., DeSouza, E.B., Vale, W.W., Struble, R.G., Whitehouse, P.J. and Price, D.L.: Evidence for structural abnormalities of corticotropin-releasing factor neurons in Alzheimer's disease. Synapse, In press.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00104-02 MPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Corticotropin-Releasing Factor as a Stress Neurotransmitter in the CNS

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	E.B. DeSouza	Chief, Neuropeptide Unit	MPL, ARC, NIDA
Others:	G. Battaglia	Staff Fellow	MPL, ARC, NIDA
	D. Price	Assistant Professor	JHU
	R. Powers		JHU
	L. Walker		JHU

COOPERATING UNITS *(if any)*

Neuropathology Laboratory, The Johns Hopkins University (JHU) School of Medicine, Baltimore, Maryland

LAB/BRANCH

Molecular Pharmacology Laboratory, Neuroscience Branch

SECTION

Neuropeptide Unit

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.8	1.4	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Corticotropin-releasing factor (CRF) is a critical hormone involved with stress responses. In addition to its role in regulating stress responses via the endocrine system, recent evidence suggests that CRF may act as a neurotransmitter in brain to integrate the overall response of the body to stress. To provide additional evidence for CRF as a neurotransmitter in brain, a series of studies was carried out in an attempt to identify receptor binding sites for CRF in the CNS. Biochemical, cellular, pharmacological and neuroanatomical approaches have been used to study the characteristics and distributions of CRF and its receptors, as well as the second messenger systems through which CRF produces its many effects. Moreover, molecular neurobiological techniques have been established to identify specific intracellular messenger RNA for CRF. High affinity binding sites for CRF have been demonstrated in brain which are distributed throughout the CNS. The anatomical distribution of these sites corresponds with the immunocytochemical distribution of CRF-containing terminals and the pharmacological sites of action of CRF in brain. In addition, it has been shown that CRF stimulates adenylate cyclase activity in rat CNS. In addition, using a combination of immunocytochemical and receptor autoradiographic techniques, it has been demonstrated that CRF is a major transmitter in the olivocerebellar pathway of humans. Also, *in situ* hybridization histochemistry has been used to localize intracellular messenger RNA for CRF in rodent and monkeys. The production of neuroanatomical maps for CRF, mRNA for CRF and CRF receptors has set the basis for subsequent studies to examine the effects of various drugs that modulate CRF neurotransmission and stress responses. It is hoped that these data will be helpful in explaining the mechanisms underlying stress responses.

Z01 DA 00104-02 MPL

Corticotropin-Releasing Factor as a Stress Neurotransmitter in the CNS

Publications

DeSouza, E.B.: Corticotropin-releasing factor receptors in the rat central nervous system: Characterization and regional distribution. J. Neurosci. 7: 88-100, 1987.

Young, III, W.S., Walker, L.C., Powers, R.E., DeSouza, E.B. and Price, D.L.: Corticotropin-releasing factor mRNA is expressed in the inferior olives of rodents and primates. Mol. Brain Res. 1: 189-192, 1986.

Powers, R.E., DeSouza, E.B., Walker, L.C., Price, D.L., Vale, W.W. and Young, III, W.S.: Corticotropin-releasing factor as a transmitter in the human olivocerebellar pathway. Brain Res. 415: 347-352, 1987.

Battaglia, G., Webster, E.L. and DeSouza, E.B.: Characterization of corticotropin-releasing factor (CRF) receptor-mediated in adenylate cyclase activity in rat brain. Synapse, In press.

DeSouza, E.B.: Corticotropin-Releasing Factor (CRF) Receptors in the Rat Central Nervous System: Autoradiographic Localization Studies. In E.D. DeSouza and C.B. Nemeroff (Eds.): Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide. Boca Raton, FL, CRC Press, In press.

DeSouza, E.B.: Corticotropin-Releasing Factor (CRF) Receptors in Brain: Characterization and Regulation. In E.B. DeSouza and C.B. Nemeroff (Eds.): Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide, Boca Raton, FL, CRC Press, In press.

Battaglia, G., Webster, E.L. and DeSouza, E.B.: Characterization of second messengers coupled to corticotropin-releasing factor (CRF) receptors in brain. In E.B. DeSouza and C.B. Nemeroff (eds.) Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide. CRC Press, Boca Raton, FL. In press.

DeSouza, E.B.: Corticotropin-Releasing Factor Receptors in Brain and Pituitary: Implications for the Stress Response. In Y. Tache (Ed.): Neuropeptides and Stress, New York, Springer-Verlag, In press.

DeSouza, E.B. and Battaglia, G.: Corticotropin-Releasing Hormone (CRH) Receptors in Brain. In G. Chroussos (Ed.): Mechanisms of Physical and Emotional Stress. New York, Plenum Press, In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00105-02 MPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cloning of Genetic Sequences for a Substance P Degrading Enzyme

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: M.M.S. Lo Chief, Molecular Biology & Genetics MPL, ARC, NIDA

Others: L.G. Sharpe Research Psychologist NPP, ARC, NIDA

COOPERATING UNITS *(if any)*

Neuropsychopharmacology Laboratory, Preclinical Branch, ARC

LAB/BRANCH

Molecular Pharmacology Laboratory, Neuroscience Branch

SECTION

Molecular Biology and Genetics

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.35	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Angiotensin converting enzyme (ACE) also functions in degrading substance P and substance K. Since these peptides, especially substance P, appear to be involved in withdrawal from chronic morphine, drugs which inhibit ACE activity might be expected to increase tissue levels of substance P, thereby potentiating withdrawal.

Captopril, an ACE inhibitor, injected 15 minutes prior to naloxone-induced withdrawal in morphine treated rats which showed increased naloxone-precipitated withdrawal. Captopril alone had no effect in morphine dependent rats. Captopril increased the occurrence of rhinorrhea, lacrimation and salivation during naloxone precipitated withdrawal. This suggests that ACE and its peptide substrates are partially involved in the expression of some opioid withdrawal behaviors.

The long-term goal of this project is concerned with cloning the genes encoding for ACE. Previous studies with primer extension using messenger RNA and a synthetic probe have provided limited sequence data for the N-terminus. Computer sequence analysis shows no close homology with other carboxypeptidases. A second probe will be synthesized and used to screen a cDNA library. It is hoped that the entire gene, comprising at least 5 kb of this enzyme, will be isolated and sequenced.

PHS 6040 (Rev. 1/84) GPO 914-918

Z01 DA 00105-02 MPL

Cloning of Genetic Sequences for a Substance P Degrading Enzyme

Publications

Sharpe, L.G., Jaffe, J.H., Lo, M.M.S. and Porrino, L.J.: Modification of naloxone-precipitated withdrawal signs by captopril and capsaicin in the morphine-dependent rat. Neurosci. Abstr., In press, 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00106-02 MPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

AIDS Related Research

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	M.M.S. Lo	Chief, Molecular Biology & Genetics	MPL, ARC, NIDA
Others:	C.M. Dersch	Chemist	MPL, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Molecular Pharmacology Laboratory, Neuroscience Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.3	1.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The primary goal of this project is to produce monoclonal antibodies to the human immunodeficiency virus (HIV). Very high affinity antibodies are selected and evaluated for their ability to directly detect the AIDS viral antigen. Antibodies are also screened for their ability to block viral binding and fusion. These antibodies may be useful in the development of vaccines.

Three sources of the HIV virus are: (a) whole inactivated virus, (b) a genetically-engineered fusion protein containing part of the HIV gp 41 produced in bacteria, and (c) envelope proteins produced in tissue culture cell lines transfected with the HIV envelope gene.

So far, several antibodies to the p24 protein have been produced. One antibody exhibits extremely high immunoreactivity. This antibody will be characterized for its binding affinity and specificity. In this regard, the method of preselected cell fusion has been found to produce superior antibodies compared with those produced by conventional methods. Thus, preselected fusion techniques are being applied to anti-HIV antigens.

Z01 DA 00106-02 MPL

AIDS Related Research

Publications

Conrad, M.K., Lo, M.M.S., Tsong, T.Y. and Snyder, S.H.: Bioselective Cell-Cell Fusion for Antibody Production. In A.E. Sowers (Ed.): Cell Fusion. New York, Plenum Press, 1987, p. 427.

Lo, M.M.S. and Tsong, T.Y.: Producing Monoclonal Antibodies by Electrofusion. In N.E. Neuman, A.E. Sowers and C. Jordan (Eds.): Electroporation and Electrofusion in Cell Biology. New York, Plenum Press, In press.

Tsong, T.Y., Tomita, M. and Lo, M.M.S.: Preselection of B-Lymphocytes by Antigen for Fusion to Myeloma Cells by Pulsed Electric Field Method. In S. Oki et al. (Ed.): New York, Plenum Press, In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00107-02 MPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Measuring Drug Receptors In Vivo and Related PET Scanning Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	M.J. Kuhar	Chief, Neuroscience Branch	MPL, ARC, NIDA
Others:	M.C. Ritz	Staff Fellow	MPL, ARC, NIDA
	M. Titeler	Associate Professor Department of Pharmacology Albany Medical School	
	H.N. Wagner	Professor	Johns Hopkins University
	D. Wong	Associate Professor	Johns Hopkins University

COOPERATING UNITS *(if any)*

Division of Nuclear Medicine, JHUMI (H.N. Wagner, D. Wong)
Department of Pharmacology and Toxicology, Albany Medical School, New York (M. Titeler)

LAB/BRANCH

Laboratory of Molecular Pharmacology, Neuroscience Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

While studying receptors by in vitro biochemical binding techniques is relatively routine, the ability to study drug receptors in vivo is a current frontier. Labeling receptors in vivo allows PET scanning studies whereby drug receptors can be measured in living human beings by this noninvasive approach.

The benzodiazepines are widely used drugs that have been abused. These drugs exert their action at a specific receptor site in the brain. Previous studies have demonstrated the ability to label these receptors in brain in vivo with a tritiated benzodiazepine drug. Recently, it has been shown that buspirone, a novel anxiolytic, increases the labeling of the benzodiazepine receptor in vivo. More extensive studies have confirmed this but have additionally shown that a variety of other drugs also cause increased labeling of this receptor. Hence, it seems that this property is not unique to buspirone and, therefore, probably not related to its novel anxiolytic action.

Since brain reward systems involve dopaminergic neurons, a thorough study of dopamine is important for understanding mechanisms of reinforcement and reward. Schizophrenics often exhibit a flat affect and lack of pleasure-seeking known as anhedonia. Since this can be considered the opposite of a drug taking experience, the density of dopamine receptors has been examined in schizophrenics using positron emission tomography scanning. It was found that these receptors are elevated in schizophrenics as suggested by in vitro biochemical studies. It is hoped that these results will ultimately contribute to understanding how dopaminergic neurons are involved in reward and reinforcement. In addition, some in vitro biochemical binding studies were conducted using N-methylspiperone, the drug used in PET scanning studies, in an effort to make quantitative interpretation of the PET scans more accurate.

Z01 DA 00107-02 MPL

Measuring Drug Receptors In Vivo and Related PET Scanning Studies

Publications

Wong, D.F., Wagner, Jr., H.N., Tune, L.E., Dannals, R.F., Pearlson, G.D., Links, J.M., Tamminga, C.A., Broussolle, E.P., Ravert, H.T., Wilson, A.A., Thomas Toung, J.K., Malat, J., Williams, J.A., O'Tunama, L.A., Snyder, S.H., Kuhar, M.J. and Gjedde, A.: Positron emission tomography reveals elevated D_2 dopamine receptors in drug-naive schizophrenics. Science 234: 1558-1563, 1986.

Lyon, R.A., Titeler, M., Frost, J.J., Whitehouse, P.J., Wong, D.F., Wagner, Jr., H.N., Dannals, R.F., Links, J.M. and Kuhar, M.J.: ^{3}H-3-N-Methylspiperone labels D_2 dopamine receptors in basal ganglia and S_2 serotonin receptors in cerebral cortex. J. Neurosci. 6(10): 2941-2949, 1986.

Goeders, N.E., Ritz, M.C. and Kuhar, M.J.: Buspirone enhances benzodiazepine receptor binding in vivo. Neuropharmacol., In press, 1987.

Kuhar, M.J.: Imaging receptors for drugs in neural tissue. Neuropharmacol. 26: 911-916, 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00108-02 MPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Cocaine Receptor

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	M.J. Kuhar	Chief, Neuroscience Branch	MPL, ARC, NIDA
Others:	M.C. Ritz	Staff Fellow	MPL, ARC, NIDA
	J. Sharkey	Visiting Fellow	MPL, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Molecular Pharmacology, Neuroscience Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.25	0.25

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

While several binding sites for cocaine have been studied, the binding site related to cocaine dependence and self-administration has not specifically been identified. Thus, in a series of binding studies, the cocaine receptor related to drug addiction and abuse has been identified. While dopamine-containing systems in the brain are known to be related to reinforcement and while it has sometimes been assumed that the inhibition of dopamine re-uptake by cocaine is the primary mechanism by which cocaine exerts its action, this has never been shown directly. That is, there has been no receptor binding data demonstrating a direct link between drug self-administration and cocaine binding to dopaminergic systems.

Recent studies in this Laboratory have shown that the potency of a variety of cocaine-like drugs in binding to the dopamine transporter is correlated with the potency of these same cocaine-like drugs in drug self-administration studies. Thus, it appears that the receptor related to cocaine dependence and self-administration is the cocaine binding site on the dopamine transporter.

In view of this demonstrated ability to study the cocaine receptor directly, the receptor is now being examined in more detail. Moreover, an attempt is being made to solubilize the receptor molecule in order to purify and sequence it. These studies may generate information about the molecular mechanism of action of cocaine.

PHS 6040 (Rev. 1/84) GPO 914-918

Z01 DA 00108-02 MPL

The Cocaine Receptor

Publications

Ritz, M.C., Lamb, R.J., Goldberg, S.R., and Kuhar, M.J.: Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science 237: 1219-1223, 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00110-02 MPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cloning of Genes Regulating the Human POMC Gene

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: M.M.S. Lo Chief, Molecular Biology & Genetics MPL, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Molecular Pharmacology Laboratory, Neuroscience Branch

SECTION

Molecular Biology and Genetics Unit

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.3	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Pro-opioimelanocortin (POMC) is an important precusor for a variety of hormones including the potent opioid peptide beta-endorphin. This project is concerned with identifying and isolating the regulatory sequences responsible for POMC expression. Various fragments from the human POMC gene were subcloned and attached to bacterial genes. Experiments using gene transfer techniques show that the POMC promotor sequence alone is insufficient for POMC expression. Other sequences are also involved in POMC expression.

Thus, an alternate approach was taken to identify this sequence. Nuclear extract from an anterior pituitary cell line (a++20) was found to protect POMC DNA from digestion with an exonuclease. However, nuclear extract from a fibroblast cell line did not protect POMC DNA from exonuclease. This confirms the existence of tissue specific nuclear proteins which recognize and bind to the POMC gene and may provide a molecular mechanism for POMC expression. The protected sequence will be subcloned and analyzed to determine its precise DNA sequence. Further evidence for the involvement of this DNA binding protein in POMC expression is shown by the enhanced protection by nuclear extracts prepared from cells treated with cyclic AMP.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00111-02 MPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cloning of Genetic Sequences Involved in the Neurotoxicity of MPP+

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	M.M.S. Lo	Chief, Molecular Biology & Genetics	MPL, ARC, NIDA
Others:	C.M. Mamalaki	Visiting Scientist	MPL, ARC, NIDA
	M.J. Kadan	Staff Fellow	MPL, ARC, NIDA
	C.M. Dersch	Chemist	MPL, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Molecular Pharmacology Laboratory, Neuroscience Branch

SECTION

Molecular Biology and Genetics Unit

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	3.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a substance of abuse, is highly neurotoxic in humans, often resulting in Parkinson's disease. MPTP is also cytotoxic to pheochromocytoma (PC12) cells. This toxicity is mediated by uptake of MPP+, the active metabolite of MPTP, into the cell. Infection of PC12 by retroviruses creates mutants which resist MPP+ toxicity. Retroviruses integrate into the chromosomes of infected cells and disrupt certain genes normally coding for proteins which are involved in MPTP toxicity. Specific biological functions are lost in these mutants.

The number of MPP+ resistant mutants infected with virus is 100 times greater than the number of resistant cells obtained by spontaneous mutation. This confirms viral infection as the direct cause of MPP+ resistance and inactivation of normal cellular genes. The phenotypes and genotypes of 36 different mutants were analyzed. Neurochemical analysis showed a distinct group of mutants which lack catecholamine uptake, whereas two other groups have either completely normal or defective dopamine uptake. Other neurochemical markers, such as choline uptake and tyrosine hydroxolase activity, appear to be normal.

In most cases, the chromosomal location of viral integrants demonstrated only a single copy of the retroviral sequence. Three distinctive chromosomal regions were found to contain the proviral sequence. These regions may contain putative genetic sequences which normally encode for proteins involved in MPTP neurotoxicity. DNA sequences from two of these gene targets were cloned and characterized by detailed restriction mapping. The presence of corresponding cellular message in normal PC12, fibroblast and tissues was analyzed by Northern blot using the cloned DNA fragments. Experimental work is currently ongoing to clone the cDNA from normal PC12 and brain tissues. The expression of these genetic sequences may identify proteins which are involved in MPTP toxicity.

Cloning of Genetic Sequences Involved in the Neurotoxicity of MPP+

The goal of this project is the ultimate identification of genetic sequences including the catecholamine uptake site and other neural proteins involved in MPTP toxicity. The catecholamine uptake site is pertinent to the study of cocaine abuse.

Publications

Lo, M.M.S., Dersch, C.M. and Mamalaki, C.: Retroviral infection in PC12 produced MPTP resistant mutants. Neurosci. Abstr., In press, 1987.

Mamalaki, C., Douglas, R.C., Carlson, S.G., Dersch, C.M. and Lo, M.M.S.: DNA sequences involved in MPTP neurotoxicity. Neurosci. Abstr., In press, 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00112-01 MPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Drug Receptors and Addiction

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	M.J. Kuhar	Chief, Neuroscience Branch	MPL, ARC, NIDA
Others:	E.B. DeSouza	Chief, Neuropeptide Unit	MPL, ARC, NIDA
	N.E. Goeders	Associate Professor Department of Pharmacology University of Louisiana	

COOPERATING UNITS *(if any)*

Department of Pharmacology, University of Louisiana, Shreveport, LA

LAB/BRANCH

Laboratory of Molecular Pharmacology, Neuroscience Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Benzodiazepine drugs are widely prescribed and often abused. They exert their actions by acting at a specific receptor found in neural tissue which is thought to be part of the GABA receptor complex. Recently a series of studies has been carried out to examine the regulation of the GABA receptor complex by steroids, hormones known to affect CNS functioning. Adrenalectomy affected GABA ratios, a measure of the coupling between benzodiazepine receptors and GABA receptors. These changes were reversed by dexamethasone. Thus, these results indicate that glucocorticoids modulate GABA receptor functioning and that receptors for important drugs can be modulated by steroids and, therefore, adrenal function can affect the actions of these drugs.

Since the action of cocaine at its receptor presumably results in potentiation of dopamine at the synapse, dopamine receptors were examined after chronic cocaine administration. After 15 days of administration of the drug, a decrease in receptors in the striatum and an increase in the nucleus accumbens (rat) was found. These data suggest that chronic cocaine administration can result in different effects on dopamine receptors in anatomically different dopaminergic systems. These effects demonstrate the importance of exerting care in drawing conclusions about the biochemical effects of cocaine, particularly regarding extrapolations to brain circuits which may be involved in reward and reinforcement.

PHS 6040 (Rev. 1/84)

GPO 814-618

Z01 DA 00112-01 MPL

Drug Receptors and Addiction

Publications:

Goeders, N.E., DeSouza, E.B. and Kuhar, M.J.: Benzodiazepine receptor GABA ratios: regional differences in rat brain and modulation by adrenalectomy. Eur. J. Pharmacol. 129: 363-366, 1986.

Goeders, N.E. and Kuhar, M.J.: Chronic cocaine administration induces opposite changes in dopamine receptors in the striatum and nucleus accumbens. Alcohol and Drug Research. 7: 207-216, 1987.

Kuhar, M.J.: Recent progress in receptor mapping: which neurons contain the receptors? Trends in Neurosci. 10: 308-310, 1987.

Jampel, H.D., Lynch, M.G., Brown, R.H., Kuhar, M.J. and DeSouza, E.B.: B-Adrenergic receptors in human trabecular meshwork. Invest. Ophthalmol. Vis. Sci. 28: 772-779, 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00113-01 MPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neurotoxicity of Selected Drugs to Monoamine Neurons in Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	E.B. DeSouza	Chief, Neuropeptide Unit	MPL, ARC, NIDA
Others:	G. Battaglia	Staff Fellow	MPL, ARC, NIDA
	R. Zaczek	Staff Fellow	MPL, ARC, NIDA
	J.C. Contrera	Pharmacologist	FDA

COOPERATING UNITS *(if any)*

Food and Drug Administration, Rockville, Maryland

LAB/BRANCH

Molecular Pharmacology Laboratory, Neuroscience Branch

SECTION

Neuropeptide Unit

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.5	2.8	0.7

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Several drugs that are currently used to treat a variety of psychiatric disorders produce their effects through actions on brain monoaminergic systems in brain. While these drugs may produce their beneficial effects through alterations in neurotransmission, the neurotoxic actions of the drugs on monoaminergic neurons following repeated use remain poorly assessed. Thus, the goal of this project is to assess the effects of chronic administration of several antidepressant and appetite suppressant drugs that are currently in clinical use or are being reviewed by the FDA relative to their possible neurotoxic effects on monoamine neurons in the brain. These drugs include fenfluramine, methylphenidate (Ritalin), pemoline (Cylert), methamphetamine, buproprion (Wellbutrinn), citalopram and paroxetine. The neurotoxic actions of these drugs will be assessed using neurochemical assays to measure changes in the concentrations of neurotransmitters and their metabolites and using radioligand binding techniques to examine alterations in monoamine uptake site density. In vitro autoradiography will be used to quantify and visualize changes in uptake site density in discrete areas of rat brain to assess whether the neurotoxic actions of these drugs are confined to certain anatomical regions. It is hoped that these studies will provide information regarding: 1) whether the drugs produce neurotoxicity (i.e., degeneration of neurons) and 2) which of the monoaminergic systems may be at risk.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA00200-02 NPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cerebral Metabolic Studies of Drug-Induced Euphoria

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	E.D. London	Chief, Neuropharmacology Lab	NPL, ARC, NIDA	
	E.P. Broussolle,	Visiting Fellow	NPL, ARC, NIDA	
Others:	J.H. Jaffe	Director, ARC	J. Links	JHMI
	R. Herning	Visiting Scientist, CHP,ARC	H.N. Wagner, Jr.	JHMI
	W. Pickworth	Scientist, CHP, ARC	R. Dannals	JHMI
	L.R. Rippetoe	Head Nurse, ARC	J.K.T. Toung	JHMI
	R.E. Johnson	Chief, RSB, ARC	D.F. Wong	JHMI

N.G. Cascella, Visiting Fellow; R.W. Margolin (Vanderbilt University)

COOPERATING UNITS *(if any)*

Biology of Vulnerability Laboratory (BVL), ARC; Cognitive Studies and Human Performance Laboratory (CHP), ARC; Research Support Branch (RSB), ARC; Vanderbilt University; The Johns Hopkins Medical Institutions (JHMI)

LAB/BRANCH

Neuropharmacology Laboratory, Neuroscience Branch

SECTION

Neuropharmacology Laboratory, Neuroscience Branch

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.2	2.2	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project uses metabolic mapping and positron emission tomography (PET) to achieve several objectives: 1) to identify brain areas or circuits related to drug-induced euphoria, 2) to assess relationships between brain metabolic and electrical activities, and 3) to correlate personality traits or cognitive deficits with brain metabolic activity. Ongoing studies focus on the metabolic effects of morphine and cocaine in an attempt to correlate changes in brain metabolism with measures of euphoria.

Human volunteers (21-45 yrs.) with an opioid abuse history, but no current drug dependencies except nicotine, participate in a double-blind, placebo-controlled, crossover study comparing morphine (M) and placebo (P) effects on the regional cerebral metabolic rate for glucose (rCMRglu) measured by the PET [^{18}F]fluorodeoxyglucose (FDG) technique. In 3 tests before PET, spontaneous EEG is recorded in addition to self reports on questionnaires and an analog scale, measuring the strength and quality of the drug effect as well as the subject's liking for the drug effect. Only subjects with positive M responses continue in the study. Positive response criteria include the following: decreased EEG alpha power or frequency or increased theta or sigma power, feeling opiate-specific sensations, recognizing M as "dope", and liking it at least slightly. Subjects fulfilling the criteria undergo 2 PET scans, usually a week apart, with 30 mg M or P given 15 min before FDG (approximately 5 mCi, i.v.), while they are blindfolded and listening to a white noise tape presenting a beep every minute. At each beep, the subject rates his euphoria on a scale of 0-4.

Cerebral Metabolic Studies of Drug-Induced Euphoria

Levels of rCMRglu are measured in 22 areas. M generally decreases rCMRglu, with significant decrements (10-15% P) in 8 areas (anterior cingulate cortex, superior & middle frontal gyri, insula, amygdalohippocampal complex, putamen, midbrain, thalamus; Hotelling's $T^2 = 43.234$, $p < .0001$). A significant correlation is obtained between temporal pole rCMRglu after M and integrated euphoria scores during the FDG incorporation period ($r = -.80$, $p = .05$). The results indicate that M decreases cerebral oxidative metabolism and implicate specific neuroanatomical sites as mediators of opioid euphoria.

Publications - FY 1987

London, E.D., Weissman, A.D., Fanelli, R.J., Wilkerson, G., Broussolle, E.P., and Jaffe, J.H.: Mapping the cerebral distribution of action of euphoriant drugs. Clin. Neuropharmacol. 9(Suppl. 4): 208-210, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00201-03 NPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cerebral Distribution & Mechanism of Action of Cocaine & MDMA ("Ectasy")

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	E.D. London	Chief, Neuropharmacology Lab	NPL, ARC, NIDA
	G. Wilkerson	Technician	NPL, ARC, NIDA
	J. Johnson	Visiting Scientist	NPL, ARC, NIDA
	A.D. Weissman	Staff Fellow	NPL, ARC, NIDA
	A.S. Kimes	Visiting Scientist	NPL, ARC, NIDA
Others:	S.R. Cohen	Visiting Fellow	NPL, ARC, NIDA
	E.B. DeSouza	Visiting Associate	MPL, ARC, NIDA

COOPERATING UNITS *(if any)*

Molecular Pharmacology Laboratory (MPL), Neuroscience Branch, ARC

LAB/BRANCH

Neuropharmacology Laboratory, Neuroscience Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.8	0.5	1.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Effects of cocaine and methylenedioxymethamphetamine (MDMA) were studied and compared. An objective was to elucidate common neurochemical actions of the drugs. Such commonalities might relate to the psychomotor stimulant and reinforcing properties of the drugs.

Cocaine stimulated local cerebral glucose utilization (LCGU) in components of the extrapyramidal motor system, but reduced LCGU in the lateral habenula of Fischer-344 and Lewis rats. It appeared that Lewis rats were more sensitive to the cerebral metabolic and behavioral effects (stereotypy) of cocaine, consistent with the view that genetic differences in sensitivity to cocaine influence the susceptibility to cocaine's abuse potential.

Ultrastructural effects of cocaine on neural tissue were studied using NG108X15 neuroblastoma cells. Cells were treated with cocaine for 1-3 days. Cocaine decreased cell viability and caused the appearance of dense bodies and nuclear abnormalities (invaginations, disruption of the nuclear membrane). The results suggest that cocaine may interfere with cell replication and may be neurotoxic.

MDMA produced marked stereotypies, and stimulated LCGU in areas associated with extrapyramidal motor, visual and limbic functions. Except for the effects in the visual system, the findings resembled those obtained with cocaine.

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00202-04 NPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effects of Acute and & Chronic Opioids & the Opioid Abstinence Syndrome

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	R.J. Fanelli	Staff Fellow	NPL, ARC, NIDA
	A.S. Kimes	Visiting Scientist	NPL, ARC, NIDA
	J.A. Bell	Pharmacologist	NPL, ARC, NIDA
	E.D. London	Chief, Neuropharmacology Lab	NPL, ARC, NIDA
	J.E. Johnson	Visiting Scientist	NPL, ARC, NIDA
Others:	E.B. DeSouza	Visiting Associate	MPL, ARC, NIDA
	M. Szikszay	Visiting Fellow	NPL, ARC, NIDA
	S.R. Cohen	Visiting Fellow	NPL, ARC, NIDA

COOPERATING UNITS *(if any)*

Molecular Pharmacology Laboratory (MPL), Neuroscience Branch, ARC

LAB/BRANCH

Neuropharmacology Laboratory, Neuroscience Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.1	1.8	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The aim of this project is to delineate physiological effects of opioids and to describe central nervous system sites that may mediate opioid agonist and antagonist effects related to somatosensory processing and the occurrence of the opioid abstinence syndrome.

Preclinical studies have shown that Ca^{2}+ channel inhibitors attenuate and delay morphine-induced respiratory depression in rats. Since this combination has also been shown to enhance opioid analgesia, the combination may reduce the dose level of opioid necessary for effective analgesia, while minimizing respiratory depression in humans. Hence, studies are planned to extend this line of reasoning in an attempt to explore mechanisms which may underlie these effects and to examine the potential applicability of these results to the human situation.

Studies were performed in rats using the deoxyglucose method to measure local cerebral glucose utilization (LCGU). Mu agonists decreased LCGU in limbic regions and several somatosensory processing areas. Nalbuphine, a kappa agonist/mu antagonist, stimulated LCGU in trigeminal nerve nuclei, suggesting that different supraspinal mechanisms mediate the actions of mu versus kappa opioids. Capsaicin, which releases substance P, stimulated LCGU in dorsal column and other brainstem nuclei, indicating that metabolic mapping might be useful in delineating the neuroanatomical areas mediating the sensory and autonomic effects of capsaicin. In animals tolerant to the analgesic effects of chronic morphine, metabolic tolerance in the brain and spinal cord was also evident. However, LCGU was stimulated in many brain and spinal cord areas during opioid abstinence. Moreover, this hypermetabolism was reversed by small doses of clonidine, an $alpha_2$-adrenergic agonist.

Physiological and Metabolic Effects of Acute and Chronic Opioids and Studies of the Opioid Abstinence Syndrome

In a parallel ultrastructural study, there was evidence of kidney degeneration in rats receiving chronic morphine, supporting the view that such changes in human addicts reflect effects of opioids per se rather than contaminants in street heroin.

Moreover, parallel electrophysiological studies provided evidence that corticotropin releasing factor (CRF) activates neurons in superficial dorsal horn presynaptic to motoneurons and directly depolarizes motoneurons. Thus, conceivably CRF could play a role in opioid abstinence.

Publications - FY 1987.

London, E.D., Fanelli, R., Szikszay, M. and Jasinski, D.: Effects of Opioid Analgesics on Local Cerebral Glucose Utilization. In J.W. Holaday, P.-Y. Law, and A. Herz (Eds.): NIDA Research Series Monograph 75. Washington, D.C., U.S. Government Printing Office, 1986, pp. 379-381.

Szikszay, M., Snyder, F.R. and London, E.D.: Effects of Morphine and Calcium Antagonists on Plasma Glucose in Male Rats. In J.W. Holaday, P.-Y. Law, and A. Herz (Eds.): NIDA Research Series Monograph. 75. Washington, D.C., U.S. Government Printing Office, 1986, pp. 382-384.

Johnson, J.E., White, J.J., Walovitch, R.C., and London, E.D.: Effects of morphine on rat kidney glomerular opdocytes: A scanning electron microscopic study. Drug Alcohol Depend. 19: 249-257, 1987.

Fanelli, R.J., Szikszay, M., Jasinski, D., and London, E.D.: Differential effects of mu and kappa opioid analgesics on local cerebral glucose utilization. Brain Res., In press.

London, E.D., Kimes, A.S. and Fanelli, R.J.: Cerebral metabolic effects of morphine in the rat. Substance Abuse, In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00206-03 NPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biochemical, Neuroanatomical & Electrophysiological Studies on Sigma & PCP Systems

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	T.P. Su	Pharmacologist	NPL, ARC, NIDA
	E.D. London	Chief, Neuropharmacology Lab	NPL, ARC, NIDA
	D.B. Vaupel	Pharmacologist	NPL, ARC, NIDA
	J.A. Bell	Pharmacologist	NPL, ARC, NIDA
	A.D. Weissman	Staff Fellow	NPL, ARC, NIDA

Others: E.P. Broussolle (Visiting Fellow), T.H. Vu (Guest Worker), NPL, ARC, NIDA; K. Marquis & J.E. Moreton (U. of MD); C.E. Spivak, Pharmacologist, NPL, ARC; J. Hedreen (JHMI);

COOPERATING UNITS *(if any)*

The Johns Hopkins Medical Institutions (JHMI) and University of Maryland (U. of MD)

LAB/BRANCH

Neuropharmacology Laboratory, Neuroscience Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.3	3.3	2.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

An endogenous ligand for sigma receptors (sigmaphin) has been further characterized. Sigmaphin was partially purified from guinea pig brain by molecular sizing and ion-exchange chromatography. The material thus obtained acted like a sigma drug (e.g., d-SKF-10047) in a bioassay system employing guinea pig vas deferens (GPVD): (1) sigmaphin potentiated electrically stimulated GPVD in a dose responsive manner with a slope parallel to that exhibited by d-SKF-10047; (2) like that induced by d-SKF-10047, the potentiation induced by sigmaphin could be reversed by putative sigma antagonists haloperidol and BW234U. Final purification of sigmaphin is being carried out.

Phencyclidine and sigma ligands were found to elicit opposite effects on local cerebral glucose utilization (LCGU). PCP increased LCGU in several specific areas in rat brain, whereas sigma ligands, such as d-SKF-10047 and DTG, selectively depressed LCGU in those areas. Behaviorally, however, no difference was observed between these groups of animals. The effects of both sigma and PCP drugs were dose-dependent. The results suggest, therefore, that the sigma and phencyclidine receptors are functionally differentiable and that those two receptors may exert opposite effects at certain points along the neuronal circuitry.

Roles of Sigma and Phencyclidine Systems: Biochemical, Neuroanatomical and Electrophysiological Studies on Sigma Receptors

Guinea pig vas deferens (GPVD) may represent a useful tool for studying sigma and phencyclidine receptors since electrically stimulated GPVD could be potentiated by sigma drugs and phencyclidine drugs. Recently, it was found that those two closely related receptors may be functionally dissected apart using the GPVD: GPVD from animals with higher body weight responded to only d-SKF-10047 and not to phencyclidine. Therefore, a functional correlation with binding affinities to either receptor may be obtained.

Publications - FY 1987

Su, T.-P.: HR375: A potential antipsychotic drug that interacts with dopamine D_2 receptors and sigma receptors in the brain. Neuroscience Lett. 71: 224-228, 1986.

Vaupel, D.B. and Su, T.-P.: Guinea pig vas deferens preparation may contain both sigma and phencyclidine receptors. Eur. J. Pharmacol. 139: 125-128, 1987.

Su, T.-P., Weissman, A.D. and Yeh, S.-Y.: Endogenous ligands for sigma opioid receptors in the brain ("sigmaphin"): Evidence from binding assays. Life Sci. 38: 2199-2210, 1986.

London, E.D., Dam, M. and Weissman, A.D.: Different Patterns of Cerebral Glucose Utilization Produced by Phencyclidine and d-N-allylnormetazocine. In E.F. Domino (ed.) Proceedings of the Second U.S.-French Sponsored Int. Seminar: Sigma Opioids/Phencyclidine-like Compounds as Molecular Probes in Biology, NPP Books, In press.

Vaupel, D.B. and Su, T.-P.: A Potential Bioassay for Identifying PCP and Sigma Ligands using the Guinea Pig Vas Deferens (GPVD). In E.F. Domino (Ed.): Proceedings of the Second U.S.-French Sponsored Int. Seminar: Sigma Opioids/Phencyclidine-like Compounds as Molecular Probes in Biology. New York, NPP Books, In press.

Weissman, A.D., Dam, M., and London, E.D.: Selective alterations in cerebral glucose utilization induced by phencyclidine. Brain Res., In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00207-03 NPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Nicotine Receptor Involvement in Behavioral & Metabolic Effects of Nicotine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	R.J. Fanelli	Staff Fellow	NPL, ARC, NIDA
	E.D. London	Chief, Neuropharmacology Lab	NPL, ARC, NIDA
Others:	E.P. Broussolle	Visiting Scientist	NPL, ARC, NIDA
	J.H. Jaffe	Director	ARC, NIDA
	J.E. Henningfield	Supervisory Pharmacologist	BDL, ARC, NIDA

COOPERATING UNITS *(if any)*

Biology of Dependence and Abuse Potential Assessment (BDL), Clinical Biology Branch, ARC

LAB/BRANCH

Neuropharmacology Laboratory, Neuroscience Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.1	0.8	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies by this Laboratory have previously demonstrated saturable, specific binding of [^{3}H]nicotine ([^{3}H]N) in the rat brain using light microscopic autoradiography. In addition, it has been shown that the distribution of the metabolic effects of nicotine follows the localization of [^{3}H]N binding sites, suggesting that the sites are functional receptors. This project is aimed at elucidating receptor mechanisms involved in the behavioral effects of chronic nicotine and at providing additional information about nicotine receptors so that it might ultimately be possible to study these receptors in the human brain with positron emission tomography (PET).

[^{3}H]l-nicotine was injected i.v. in mice which were killed at various times. Brains were dissected for measurement of radioactivity. Nonspecific binding was determined in mice pretreated with unlabelled l-nicotine. There was a rapid entry of [^{3}H]N into the brain (maximum at 5 min.) and specific binding was heterogeneously distributed with, for example, levels highest in medial and posterior cortex and thalamus/hypothalamus, intermediate in frontal cortex, cerebellum and caudate-putamen, and lowest in hippocampus and olfactory bulb. Nicotinic agonists significantly inhibited binding while several nicotinic antagonists were inactive. These results suggest that specific binding of [^{3}H]N can be measured in vivo with radiolabelled nicotine.

Studies of Nicotine Receptors and Their Involvement in the Behavioral and Metabolic Effects of Nicotine

Since nicotine is self-administered chronically, it is important to know its effects of brain function following repeated administration. Thus, animals were treated chronically (10 days) with nicotine and local cerebral glucose utilization was measured. While behavioral tolerance to this treatment was not clearly evident, several brain regions, including the anteroventral thalamus and sustantia nigra pars compacta, showed metabolic evidence of tolerance. In other groups of animals, additional brain regions provided evidence that is consistent with signs of withdrawal and receptor upregulation. The analyses of receptor dynamics and behavior are currently underway. These findings may contribute valuable insights into the understanding of cerebral mechanisms associated with tolerance and withdrawal associated with nicotine.

Publications - FY 1987

Henningfield, J.E., London, E.D. and Jaffe, J.H.: Nicotine Reward: Studies of abuse liability and physical dependence potential. In J. Engle and L. Oreland (Eds.): Brain Reward Systems and Abuse. New York, Raven Press, 1987, pp. 147-164.

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00208-03 NPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cerebral Metabolic Studies of Anxiolytics

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	E.D. London	Chief, Neuropharmacology Lab	NPL, ARC, NIDA
Others:	M. Dam	Visiting Scientist	NPL, ARC, NIDA
	E.P. Broussolle	Visiting Fellow	NPL, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropharmacology Laboratory, Neuroscience Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.4	0.3	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The 2-deoxy-D-[1-^{14}C]glucose ([^{14}C]DG) method was used to assess acute effects of diazepam and CL 218,872 on local cerebral glucose utilization (LCGU) in awake rats. Diazepam, 2.5 mg/kg, i.v., 2 min. before [^{14}C]DG, decreased LCGU in 15 of 61 brain regions examined, but increased LCGU in the superior colliculus. A higher dose (5 mg/kg) of diazepam produced greater decrements and affected more areas. Most LCGU effects of 5 mg/kg diazepam occurred at 2 min., and were also seen in rats treated 30 min., but not 180 min., before [^{14}C]DG. LCGU decrements occurred preferentially in areas rich in type I benzodiazepine receptors (cerebellum, globus pallidus, thalamus, cerebral cortex) compared to those with high densities of type II receptors (caudate-putamen, nucleus accumbens, dentate gyrus). An i.p. treatment with 5 mg/kg CL 218,872, 30 min. before [^{14}C]DG, did not affect LCGU, but 10 mg/kg reduced LCGU in a pattern which resembled the effects of diazepam. Exceptions were seen in the globus pallidus, in which diazepam, but not CL 218,872, reduced LCGU, and the dentate gyrus, in which CL 218,872, but not diazepam, reduced LCGU at the dosages used. The findings provide information about neuroanatomical sites that may be important to the behavioral effects of diazepam and CL 218,872 and are consistent with a functional distinction between type I and type II benzodiazepine receptors.

Scheduled activity in this project for FY 88 is preparation of research findings for publication.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00209-04 NPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Factors Which Influence Rates of Local Cerebral Glucose Utilization (LCGU)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	E.D. London	Chief, Neuropharmacology Lab	NPL, ARC, NIDA
Others:	I.R. Cohen-Becker	Research Fellow	Univ. of MD
	N.G. Weiland	Research Fellow	Univ. of MD
	P.M. Wise	Professor	Univ. of MD
	M. Selmanoff	Associate Professor	Univ. of MD
	R. Walovitch	Research Pharmacologist	NEN Corp.
	S.R. Cohen	Visiting Fellow	NPL, ARC, NIDA

COOPERATING UNITS *(if any)*

Department of Physiology, University of Maryland (Univ. of MD), New England Nuclear Corp. (NEN Corp.)

LAB/BRANCH

Neuropharmacology Laboratory, Neuroscience Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.9	0.5	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Regional or local cerebral glucose utilization (rCMRglu and LCGU, respectively) are used extensively as indices of brain function. Therefore, it is important to consider the potential influences of various physiological and psychological factors on cerebral glucose utilization in interpretations of psychoactive drug effects on brain metabolism. Studies of the effects of various conditions on LCGU have been initiated in the rat. Factors considered to date include age, endocrine status, circadian periodicity, restraint stress, and pain.

Questions addressed included the effects of prolactin, restraint stress, and several pain models on LCGU. Hyperprolactinemia was associated with decreased LCGU in the medial forebrain bundle and the dorsal hippocampus. Free-ranging rats had significantly higher rates of LCGU than restrained rats in several areas including the medial septal nucleus, rostral striatum, frontoparietal cortex, and median eminence. The results indicate that hyperprolactinemia may be associated with inhibition of the brain areas that project to the median eminence, where prolactin stimulates dopamine turnover, and that restraint is a factor which could influence LCGU. Neither the formalin nor the tail immersion models of pain produced statistically significant alterations in LCGU.

Studies in young and old ovariectomized rats demonstrated a diurnal rhythmicity in LCGU of the suprachiasmatic nucleus and pineal gland in young and old animals. Although there was no age difference in LCGU in the pineal gland, LCGU was reduced during the light and dark in all hypothalamic areas examined except the suprachiasmatic preoptic nucleus and the median eminence. Middle-aged rats primed with estradiol showed an irregularity in the circadian periodicity of LCGU in the suprachiasmatic nucleus, associated with a loss of cyclic reproductive function. The scheduled activity in this project during FY88 is publication of the research findings.

Z01 DA00209-04 NPL

Factors Which Influence Rates of Local Cerebral Glucose Utilization (LCGU)

Publications - FY 1987

Selmanoff, M., Walovitch, R.C., Walder, G.E., and London, E.D.: Effects of hyperprolactinemia on plasma prolactin and glucose and on local cerebral glucose utilization. J. Neurochem. 48: 94-101, 1986.

Walovitch, R.C., Ingram, D.K., Spangler, E.L. and London, E.D.: Co-dergocrine, cerebral glucose utilization and maze performance in middle-aged rats. Pharmacol. Biochem. Behav. 26: 95-101, 1986.

Waller, S.B. and London, E.D.: Noninvasive Diagnostic Techniques to Study Age-Related Cerebral Disorders. In M. Bergener (Ed.): Psychogeriatrics, An International Handbook. New York, Springer, 1987, pp. 172-193.

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00210-02 NPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effects of Chronic Drug Abuse on Lymphoid and Brain Receptors

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	A.S. Kimes	Visiting Scientist	NPL, ARC
	E.D. London	Chief, Neuropharmacology Lab	NPL, ARC
Others:	W.J. Smith	The Johns Hopkins Medical Institutions	

COOPERATING UNITS *(if any)*

The Johns Hopkins Medical Institutions, Baltimore, Maryland

LAB/BRANCH

Neuropharmacology Laboratory, Neuroscience Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	0.6	0.9

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Intravenous drug abusers are at high risk for acquired immunodeficiency syndrome (AIDS), suggesting that chronic exposure to abused substances may alter immune function. As morphine is commonly abused by intravenous injection, the effect of chronic treatment with this opioid in mice is being measured by three techniques: 1) flow cytometry and monoclonal antibodies to detect relative numbers of subpopulations of peripheral blood T-lymphocytes (in collaboration with Dr. W.J. Smith), 2) the response of splenocytes to mitogen stimulation (in collaboration with Dr. W.J. Smith), and 3) densities and affinities of splenocyte receptors for neuroactive substances which may be involved in immune function.

Morphine treated mice have fewer circulating T-lymphocytes (helpers and suppressor/cytotoxic) than concurrent controls. The effect is dose-dependent and is correlated with lower spleen/body weight ratios and white cell counts but not blocked by the opioid antagonist naltrexone and not produced by the mu opioid agonist oxymorphone. Morphine treatment has no effect on mitogen-stimulated lymphocyte proliferation. Scatchard analysis and displacement studies of the sigma receptor in mouse splenocytes demonstrate that this receptor has binding characteristics that are similar but not identical to sigma receptors in other species. Preliminary results suggest a reduction in the number of sigma binding sites on mouse splenocytes associated with chronic morphine treatment. Other receptor binding assays are being developed. The specificity of morphine's effect on immune function will be examined using other opioids used by members of the high risk group such as heroin, methadone, and buprenorphine. This work suggests that morphine compromises immunocompetency. The use of morphine by intravenous drug abusers, therefore, may increase the incidence of infection subsequent to exposure to bacterial and viral agents (i.e. AIDS).

PHS 6040 (Rev. 1/84)

GPO 814-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00212-03 NPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

In Vivo and In Vitro Studies of Kappa Receptors

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	T.-P. Su	Pharmacologist	NPL, ARC, NIDA
	E.D. London	Chief, Neuropharmacology Lab	NPL, ARC, NIDA
	D.B. Vaupel	Pharmacologist	NPL, ARC, NIDA
Others:	C. Ori	Visiting Fellow	NPL, ARC, NIDA
	P.R. Oeltgen	Associate Professor	Univ. of Kentucky
	D.S. Bruce	Professor	Wheaton College

COOPERATING UNITS *(if any)*

University of Kentucky
Wheaton College

LAB/BRANCH

Neuropharmacology Laboratory, Neuroscience Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.2	0.3

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Chronic infusion of naloxone in summer active ground squirrels antagonized hibernation induced by a hibernation induction trigger (HIT) isolated from winter hibernating woodchucks. The possible involvement of kappa opioid receptors in HIT-induced hibernation was examined, using a kappa selective ligand, U69593. U69593 did not induce hibernation, but antagonized HIT-induced hibernation. Thus, HIT may induce hibernation through interactions with non-kappa opioid receptors (e.g., mu, sigma). U69593-induced antagonism of hibernation suggests that kappa receptors may be involved in the arousal state of animal hibernation.

In studies of kappa receptors in human neuropsychopathological conditions, it is important to know the biochemical stability of kappa receptors under storage conditions simulating those to which human autopsy material is subjected. A study using guinea pig brains demonstrated an extraordinary stability of kappa receptors. The kappa receptor is stable for up to 16 hours under such storage conditions.

One possible mechanism of action of anesthetics is alteration of neurotransmitter receptor binding. Effects of N_2O and halothane on mu and kappa receptors were examined. N_2O increased Kd's for mu and kappa receptors, and decreased Bmax of kappa binding. Halothane increased Kd for mu receptors but decreased Kd for kappa receptors with a concomitant decrease in Bmax. Thus, volatile anesthetics affect mu and kappa opioid receptors.

The effects of a kappa peptide BW942C on urine output were examined in humans, rats and squirrel monkeys. BW942C bound to mu, kappa and sigma receptors, was diuretic at low doses and antidiuretic at higher doses. The antidiuretic effect was antagonized by low doses of naltrexone; but the diuretic effect, which was less efficacious than that of the kappa drug, U50488, was antagonized by high doses of naltrexone. The results suggested that BW942C is a partial kappa agonist and a mu agonist.

Z01 DA00212-03 NPL

In Vivo and In Vitro Studies of Kappa Receptors

Publications - FY 1987

Bruce, D.S., Cope, G.W., Elam, T.R., Ruit, K.A., Oeltgen, P.R. and Su, T.-P.: Opioids and hibernation. I. Effects of naloxone on bear "Hibernation Induction Trigger's" depression of guinea pig ileum contractility and on induction of summer hibernation in the ground squirrel. Life Sci., In press.

Oeltgen, P.R., Welborn, J.R., Spurrier, W.A., Bruce, D.S. and Su, T.-P.: Opioids and hibernation. II. Effects of kappa opioid U69593 on induction of hibernation in summer active ground squirrels by "Hibernation Induction Trigger" (HIT). Life Sci., In press.

Ori, C., Su, T.-P., Weissman, A.D. and London, E.D.: Extraordinary postmortem stability of kappa opioid receptors in guinea pig brain. J. Pharm. Pharmacol., In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00217-03 NPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Structures and Activities of Semirigid Nicotine Agonists

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	C.E. Spivak	Pharmacologist	NPL,ARC,NIDA
Others:	J.A. Waters	Chemist	NIH
	T.M. Gund	Chemist	New Jersey Inst. Tech.
	K. Maglesby	Biophysicist	Univ. of Miami
	R. Aronstam	Biochemist	Med. College of Georgia
	I. Stolerman	Pharmacologist	Inst. Psychiatry, De Crespigny Park, London

COOPERATING UNITS *(if any)*

NIH, New Jersey Institute of Technology, University of Miami, Medical College of Georgia, Institute of Psychiatry, De Crespigny Park, London

LAB/BRANCH

Neuropharmacology Laboratory, Neuroscience Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.6	0.6	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project aims at understanding one of the most fundamental problems in neurobiology and pharmacology, molecular recognition. It employs the nicotinic acetylcholine receptor, which is the best understood receptor for neurotransmitters. New agonists, synthesized in this laboratory and by Dr. J. Waters, include ring structures to enforce a semirigid shape. Further, refinements in learning the agonists' conformations and electrostatic energy profiles are calculated by Dr. Gund.

The receptor reacts to agonists by directly opening a cation channel. The "patch clamp" technique permits one to record the few picoamps of current that traverse this channel. The durations of open and closed channels yield kinetic information on the linkage between the drug and the ion channel. In fiscal year 87, patch clamp experiments were concluded on the two most potent drugs of the series, isoarecolone methiodide and dihydroisoarecolone methiodide. Dr. Karl Magleby is providing assistance in analyzing the data by unique means developed in his laboratory. Though still incomplete, the analysis is yielding unexpected findings: 1) the existence of a third, previously unknown, open state of the junctional ion channel, and 2) that the kinetics of activation of the ion channel induced by these two drugs is so similar that their 5-fold difference in potency must be due, by exclusion, to differences in rates at which they desensitize the receptor.

Behavioral and binding experiments with isoarecolone and its methiodide were done with Drs. Stolerman and Reavill using rats. Binding studies of all the agonists of the isoarecolone methiodide series were done with Dr. Aronstam using electric organ from Torpedo as a source of nicotinic receptors and rat forebrain as a source of muscarinic (M1) receptors.

GPO 814-918

Z01 DA00217-03 NPL

Structures and Activities of Semirigid Nicotine Agonists

Publications - FY 1987

Reavill, C., Spivak, C.E., Stolerman, I.P., and Waters, J.A.: Isoarecolone can inhibit nicotine binding and produce nicotine-like discriminative stimulus effects in rats. Neuropharmacol. 26: 789-792, 1987.

Waters, J.A., Spivak, C.E., Hermsmeier, M., Yadav, J.S., Liang, R.F. and Gund, T.M.: Synthesis, pharmacology and molecular modeling studies of semirigid, nicotinic agonists. J. Med. Chem. In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA00002-07 NPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Assessment of the Abuse Liability of PCP-like Compounds

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	D.B. Vaupel	Pharmacologist	NPL,ARC,NIDA
Others:	H.E. Shannon	Pharmacologist	NPP,ARC,NIDA
	M. Risner	Research Psychologist	BPL,ARC,NIDA

COOPERATING UNITS *(if any)*

Neuropsychopharmacology (NPP) and Behavioral Pharmacology (BPL) Laboratories, Preclinical Pharmacology Research Branch

LAB/BRANCH

Neuropharmacology Laboratory, Neuroscience Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Experiments were conducted to evaluate the degree of phencyclidine (PCP)-like activity associated with the dextro and levo enantiomers of the o agonist N-allylnormetazocine (NANM). In chronic spinal dogs, d- and l-NANM generally produced similar physiologic and gross animal behavior effects which included mydriasis, tachycardia, hyperthermia, increased secretory activity (lacrimation, rhinorrhea and salivation), nystagmus and stereotyped head movements. For these effects, d- and l-NANM were generally equal in potency and both were about 1/10th as potent as PCP. However, the NANM enantiomers could be differentiated on the basis of their effects on nociceptive reflexes. Comparisons of dose-response curves and efficacies demonstrated that d-NANM was more similar to PCP in its effectiveness in depressing flexor and skin twitch reflexes than was l-NANM. In addition, naltrexone selectively antagonized or reduced only the effects of l-NANM on reflex activity. In intact dogs, d-NANM and PCP, but not l-NANM maintained self-administration behavior under FR15 or FI900 (FR10:S) schedules of reinforcement. This represented the most stereospecific action of the NANM enantiomers. Additionally, l-NANM failed to maintain self-administration behavior, even following pretreatment with naltrexone, thus suggesting that the opiate activity of l-NANM was not responsible for its lack of reinforcing efficacy. Taken together, the data demonstrate that both d- and l-NANM have PCP-like properties, but d-NANM is pharmacologically more equivalent than l-NANM to PCP and l-NANM has additional activity which is not PCP-like. (Formerly, Z01 DA00002-06 NPP).

Z01 DA00002-07 NPL

Assessment of the Abuse Liability of PCP-like Compounds

Publications - FY 1987

Vaupel, D.B., Risner, M.E. and Shannon, H.E.: Pharmacologic and reinforcing properties of phencyclidine and the enantiomers of N-allylnormetazocine in the dog. Drug and Alcohol Depend. 18: 173-194, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00003-03 NPL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Investigations of Kappa and Sigma Properties of Antinociceptive Drugs in the Dog

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	D.B. Vaupel	Pharmacologist	NPL, ARC, NIDA
Others:	E. Cone	Senior Scientist	CDM, ARC, NIDA
	B. Nickel	Research Associate	Degussa Pharmaceuticals

COOPERATING UNITS *(if any)*

Degussa Pharma, Frankfurt, West Germany, Laboratory of Chemistry and Drug Metabolism, Clinical Biology Branch, ARC

LAB/BRANCH

Neuropharmacology Laboratory, Neuroscience Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

It was previously demonstrated that the pharmacologic activity of d,l-ketocyclazocine is associated with the l-enantiomer; the d-form being inactive. To show that the actions of l-ketocyclazocine represent kappa and not mu effects, selective antagonism studies with naltrexone were conducted. Low doses of naltrexone (0.01 mg/kg) antagonized morphine whereas high doses (1 mg/kg) were needed to antagonize d,l-ketocyclazocine, thus demonstrating that the agonist actions of d,l-ketocyclazocine can be classified as of the kappa type in the chronic spinal dog.

Flupirtine is a new analgesic whose mechanism of action is unknown. To assess the role of opioid mechanisms in flupirtine-induced antinociception, flupirtine was compared to the opioid pentazocine using both single dose and naltrexone antagonism studies in the chronic spinal dog. It was concluded that flupirtine-induced antinociception is not opiate receptor mediated and occurs primarily at supraspinal sites. Its antinociceptive potency was estimated to be 1/12th that of pentazocine in the dog.

The acute interactions of pentazocine and tripelennamine, in ratios that have been abused by humans, have been evaluated in the chronic spinal dog. No consistent pattern among the interactions emerged. Depending on the parameter, the interactions showed that tripelennamine's effects summated algebraically with or antagonized the effects of pentazocine. Naltrexone antagonized pentazocine but not tripelennamine and tripelennamine failed to antagonize the sigma-like activity of SKF-10047. While such interactions may contribute to the abuse liability of tripelennamine and pentazocine, the tripelennamine component is not opiate-like and tripelennamine does not antagonize sigma activity, which has been suggested to be a canine model for dysphoria. (Formerly Z01 DA00003-02 NPP).

Psychopathology and Cognitive Studies Branch

Jerome H. Jaffe, M.D., Acting Chief

Overview

The Psychopathology and Cognitive Studies Branch currently consists of two laboratories: Cognition/Human Performance and Psychology of Vulnerability.

The Psychology of Vulnerability Laboratory attempts to identify mechanisms by which risk factors such as aggressiveness and impulsivity may contribute to later drug abuse problems. During this past year, the Laboratory had only one full-time staff fellow and a visiting fellow; a full-time chief has not yet been recruited. Its report remains brief. Nevertheless, some preliminary studies on neuroendocrine correlates of aggressivity and impulsivity have been conducted and have yielded interesting findings. Most of its studies are carried out in collaboration with other laboratories such as Biology of Vulnerability and Cognition/Human Performance.

The second Laboratory, Cognition/Human Performance, was established in recognition of the increased emphasis society is placing upon the cognitive and performance impairments produced by the use of psychoactive drugs, and in response to the ARC's responsibility under arrangements with the Department of the Army to study the effects of cholinergic blocking agents on human cognition and performance. Another major mission of the Laboratory is to apply newer computerized electrophysiological techniques to the assessment of individual differences associated with risk factors for drug abuse and with altered psychological and physiological functioning during drug withdrawal syndromes. During the last year, Dr. Ronald Herning, a Visiting Scientist, has been functioning as its principal scientist.

Psychology of Vulnerability Laboratory — Jerome H. Jaffe, M.D., Acting Chief

Overview

The major mission of this Laboratory is the study of psychological and physiological factors that heighten risk for drug abuse and dependence. Research in this Laboratory is performed using several different designs: 1) behavioral genetic designs to separate genetic from environmental factors as risks for later drug abuse, 2) drug conditioning paradigms to separate learning factors from pharmacological factors in drug dependence, and 3) psychophysiological approaches that examine correlations among dimensions of personality, diagnostic characteristics and biological parameters thought to be related to heightened risk for drug abuse and dependence. In addition, the Laboratory plays a key role in focusing the attention of all ARC investigators on psychological factors by systematically obtaining data on psychological function and psychiatric diagnosis on all subjects recruited for inpatient studies at the ARC.

Current research efforts focus on the development and utilization of psychodiagnostic and electrophysiological measures in studies of adolescent and adult populations that are drug dependent or at heightened risk for dependence. Based on earlier results from study of adolescents with high rates of delinquency, the Laboratory began work with an adult drug dependent population. This research investigated the relationship between drug dependence/abuse and psychiatric classification, emotional distress, aggression and psychopathy.

Most of the major projects carried out by the Laboratory are interdisciplinary studies and involve collaboration with other laboratories, particularly in areas that involve drug administration, and electrophysiological and neuroendocrine assessments.

The Laboratory has been expanded recently by the addition of two investigators, Drs. David Newlin and Craig Nagoshi, who are developing research initiatives to study risk for drug abuse in monozygotic and dizygotic twins, as well as family history and personality factors in sensitivity and tolerance to different drugs of abuse.

Cognition and Human Performance Laboratory — Ronald Herning, Ph.D., Acting Chief

Overview

The Cognition and Human Performance Laboratory uses psychophysiologic, neurophysiologic and cognitive approaches to identify biological markers in populations at risk for drug abuse, cognitive and performance deficits produced by drugs of abuse, and deficits occurring during withdrawal which may prevent or interfere with effective behavioral performance or drug cessation treatment. Specific research projects include studies to assess the effects of drugs of abuse on sensory and cognitive information processing, memory, attention, habituation, behavioral performance, and motor performance, and to relate these findings to (1) drug altered performance in the work place, (2) effective intervention and prevention strategies as well as to identify psychophysiologic and cognitive markers in populations at risk for drug abuse, and (3) neurophysiological mechanisms of cognitive drug reinforcement.

The Cognition and Human Performance Laboratory collaborates with the Psychology of Vulnerability, the Biology of Vulnerability, and the Biology of Dependence and the Neuropharmacology Laboratories. These collaborations include the continuation of some studies begun in the previous year and several new studies. The new studies include (1) the electrophysiologic effects of cocaine and drugs which might block the CNS effects of cocaine, (2) the relationship between the electrophysiologic, cerebral metabolic (as measured by Positron Emission Tomography) and subjective effects of cocaine, and (3) the effects of cholinergic agents on the behavioral and neurophysiologic indices of cognitive information processing. Two new collaborative studies were begun with the Treatment and Early Intervention Branch. The first study monitors neurophysiologic and cognitive processing in persons withdrawing from cocaine; sleep and activity patterns are also being monitored. In the second treatment study, the neurophysiologic and cognitive effects of buprenorphine maintenance and buprenorphine withdrawal are being monitored.

Over the past year, the Laboratory has upgraded its sensory cognitive neurophysiologic test battery. Nine new test procedures were added. Topographic mapping of multichannel EEG and evoked potential data has enhanced data analysis capacity. These color maps of electrical activity from the head during resting and cognitive processing will aid in localization of drug effects in the human brain. The new technical advances will also aid in the quantification of drug-produced alteration in cognition and performance, the characterization of cognitive and performance deficits observed during drug withdrawal, the evaluation of sensory and cognitive information processing abilities in populations at risk for drug abuse, and the investigation of drug effects on the brain electrical activity as both a correlate and as a probe to delineate drug-related activity.

Summary of Ongoing Research

Cocaine Studies

Over the past year, three new studies were started to investigate the effects of cocaine or cocaine withdrawal on human neurophysiology and cognition were initiated. Earlier studies found that cocaine increased EEG beta, blood pressure, pulse and subjective feeling of "rush". The temporal sequence of the onset and offset of these measures has not been investigated, but could provide valuable information as to the mechanisms by which cocaine produced its euphorigenic effects. Likewise, pretreatment by an appropriate blocking drug might either block all of cocaine effects or selectively alter the time course and magnitude of some of these effects. However, in both cases the desirability of the drug might be reduced and its mechanism of action clarified.

In a newly devised study, the onset and time course of cocaine's effects was precisely measured after intravenous cocaine while collecting CNS, cardiovascular and subjective measures. Various calcium channel blockers are being used as pretreatment in an attempt to antagonize the effects of cocaine. The results of this study may be of theoretical and practical importance. Five subjects have been tested thus far with one calcium channel blocker, nifedipine.

In a second new study, the effects of cocaine on multichannel EEG are compared with regional cerebral glucose utilization measured with Positron Emission Tomography (PET) in humans. Both techniques provide critical information regarding the localization of the effect of cocaine on the brain. Collaboratoring investigators are performing the PET scans which can only provide regional cerebral glucose utilization for a time interval that is at least 10-15 minutes in length. The EEG measures supplement the PET data by providing cortical electrical data at intervals as short as one second. Thus, if a cortical area is involved in the euphoria state produced by cocaine, or if they reflect the activity of subcortical structures, the EEG will provide the time course as well as some suggestions about the brain areas involved in the cocaine produced activity. Two subjects have been tested in this protocol thus far. The subjects tested showed an increase in EEG beta in the temporal cortex and an increase in EEG alpha in the frontal and parietal cortices after 40 mg of intravenous cocaine as compared to an intravenous placebo.

The third study monitors aspects of cognition and behavioral performance as well as sleep patterns in heavy intravenous cocaine users withdrawing from cocaine. Information processing deficits were observed in heavy cocaine users in withdrawal in earlier studies. Complaints of sleep loss were also reported, but not well documented. Both information processing deficits and sleep loss are likely to interfere with effective treatment and perhaps contribute to relapse. In cocaine users not seeking treatment, cyclic periods without cocaine may produce impaired job performance. The current study was designed to carefully document cognitive processing alterations

during cocaine withdrawal with a combination of sensitive behavioral tasks and cognitive event related potential measures. These tasks measure attention, stimuli evaluation memory, vigilance, responsive to task relevant rare events and visual motor tracking. Sleep and awake periods are monitored by a wrist activity meter. Sleep EEG patterns will also be collected in a subset of these subjects. Although not all the subjects were tested and not all the data has been analyzed, the activity meter data indicated a disrupted sleep and event related potential data suggest an impairment of attention followed by an improved stimulus processing in the first three weeks of cocaine withdrawal.

Opioid Studies

The characterization of electrical activity produced by mu, kappa and sigma opiate agonist has continued from the previous fiscal year into the current fiscal year. The emphasis in the current year has been the characterization of sigma opiate effects elicited by pentazocine-naloxone combinations. Several additional subjects have been tested in a two phase six day study. Pentazocine (70 mg) and pentazocine (70 mg) with 15 mg of naloxone have been used (1) to replicate the purported sigma effect on the spontaneous EEG, (2) study the effects of sigma agonist on information processing, and (3) characterize the sigma agonist-induced subjective state. The effects of morphine on scalp EEG and regional cerebral glucose utilization have been continued. EEG and PET scan are being compared to further trace the location of morphine effects in the brain.

In a treatment study which began in this fiscal year, the effects of buprenorphine maintenance and subsequent buprenorphine withdrawal were investigated in heroin users. Various aspects of cognition were measured using a battery of cognitive tasks throughout the maintenance and withdrawal phases. In some of the tasks, neurophysiologic measures of cognitive information processing supplemented the behavioral measures of cognitive performance. Pupil size and the pupillary light reflex were also measured. Seven subjects have completed the protocol.

The specific aim of the cognitive testing is to determine whether there are severe cognitive deficits when addicts are dosed every other day with buprenorphine. The testing during withdrawal is designed to determine the extent and time course of cognitive disruption during buprenorphine withdrawal.

Effects of Benzodiazepines and Anticholinergic Agents on Sensory and Cognitive Information Processing

Under a grant from the Department of the Army, subject testing was completed in a study exploring the effects of benzodiazepines on sensory and cognitive information processing. A battery of sensory and cognitive neurophysiological tasks was used to assess sensory, cognitive and performance deficits produced by multiple doses of diazepam. The purpose of the study was to determine by electrophysical methods where in the information processing sequence the benzodiazepines exert their effects.

Deficits in memory have previously been noted. Preliminary results suggest that stimulus evaluation processes were impaired at higher doses. Thus, the effects of diazepam on memory may be due to a failure to encode the task relevant stimuli rather than a failure to remember the encoded information. Significant changes were also observed in the resting EEG. Further data analysis is required.

An additional study for the military during the current year examined physostigmine's effects on basic sensory electrophysiology and cognitive information processing. Physostigmine was compared to placebo with and without pretreatment with methscopolamine (5 mg). The tasks included eyes open EEG, physiological tremor, pattern reversal visual evoked response, self-paced motor potential rare event monitoring and Sternberg memory tests. Nine subjects have been tested with continued testing expected. Preliminary data suggest that stimulus evaluation is enhanced by this dose of physostigmine. The enhancement is not blocked by methscoplamine. Data from other tasks requires further analysis.

Vulnerability Studies

Many factors appear to be important in the etiology of drug abuse. Both antisocial behavior and early aggression are risk factors for later drug use. During the preceding fiscal year, information processing was studied in two groups of non-institutionalized adolescents. The more delinquent group (N=12) was selected because of school related conduct problems. The less delinquent group (N=13) was age, IQ, race and neighborhood matched groups of adolescents. Spontaneous EEG's and event related potentials were recorded from the scalp and extensive psychometric data were obtained. Both sensory and cognitive information processing deficits were observed in the more delinquent group. The latency of Wave V of auditory brainstem-evoked response was delayed, N100 latency was decreased and frontal slow wave was absent in the more delinquent individuals. Further data analysis indicated that P300B, a measure of stimulus evaluation, was reduced in all adolescents who used illicit drugs regardless of their history of aggression.

In an ongoing project, the Laboratory collaborates with several other laboratories in measuring biological markers of impulsivity and/or aggression. Volunteers with varied drug abuse histories are assessed using a number of psychiatric and personality batteries. They are subsequently challenged with pharmacological probes and an oral glucose load while neuroendocrine subjective and electrophysiological measures are made. Thus far 25 subjects have completed the study. Preliminary results are described under the activities of Biology of Vulnerability.

Nicotine Studies

During the current year, the Laboratory's efforts were also directed toward the analysis of a major study investigating tobacco withdrawal in heavy smokers. The EEG, cognitive and performance measures were used to examine cognitive processing during a ten day period of tobacco withdrawal in heavy smokers. Subject testing ended in the previous fiscal year. Data analysis

began during the current year. Preliminary data indicate changes persisted over the entire ten day deprivation period. These measures included EEG alpha frequency, theta power, performance on a selected computerized cognitive task (rapid automatic task) and N100 amplitude (a cognitive evoked potential). Stimulus evaluation time as measured by P300 latency, the depth of stimulus evaluation as measured by P300 amplitude, and simpler tasks on the computerized cognitive battery were affected only early during the tobacco deprivation period.

Cognitive deficits are clearly apparent during nicotine abstinence and they may contribute to relapse during treatment. During nicotine withdrawal the deficits have two different time courses: one which dissipates after 5 to 7 days and one which persists at least 10 days. The first appears to affect stimuli evaluation and the second affects selective attention. The efficiency of nicotine gum in relieving these cognitive deficits was also investigated, but these results are not yet fully analyzed.

Publications FY 87-88

Publications - Journal Articles

Herning, R.I., Hunt, J.S. and Jones, R.T.: Speech event related potentials reflect linguistic content and processing level. Brain and Lang. 30: 116-129, 1987.

Herning, R.I., Hooker, W.D. and Jones, R.T.: Cocaine effects on electroencephalographic cognitive event related potentials and performance. Electroencephalogr. Clin. Neurophysiol. 66: 34-42, 1987.

Herning, R.I., Speer, M. and Jones, R.T.: Event-related potentials to spoken equations: Is the N400 really a late N200. Electroencephalogr. Clin. Neurophysiol., In press, February, 1987.

Publications - Abstracts and Short Papers

Broussolle, E., London, E.D., Links, J., Wong, D.F., Dannals, R.F., Wagner, H.H., Rippetoe, S., Holicky, B., Herning, R.I., Pickworth, W.B., Toung, J.K.T. and Jaffe, J.H.: Morphine-induced decreases in regional cerebral glucose utilization in human post addicts. Soc. Nuc. Med., June, 1987.

Pickworth, W.B., White, B. and Herning, R.I.: Atropine effects on spontaneous electroencephalogram (EEG) in humans. Proc. Sixth Med. Chem. Def. Biomed. Rev. 1987, pp. 641-646.

Herning, R., Pickworth, W., Glover, B., Richards, L. and Arnold, P.: The effects of atropine on EEG indices of cognitive information processing. Proc. Sixth Med. Chem. Def. Biomed. Rev. 1987, pp. 647-650.

Pickworth, W.B., Herning, R.I., Henningfield, J.E.: Mecamylamine reduces some EEG effects of nicotine gum in humans. Pharmacol. Biochem. Behavior, Submitted.

Broussolle, E., London, E.D., Links, J., Wong, D.F., Dannals, R.F., Wagner, H.N., Rippetoe, S., Holicky, B., Herning, R.I., Pickworth, W.B., Toung, J.K.T. and Jaffe, J.H. Morphine-induced decreases in regional cerebral glucose utilization in human postaddicts. Soc. Nuc. Med. 34th Annual Convention, Toronto, Ontario, June, 1987, In press.

Pickworth, W., White, B. and Herning, R.I.: Atropine effects on spontaneous electroencephalogram in humans. Sixth Chemical Reference Bioscience Review, Johns Hopkins University Applied Physics Laboratory, Columbia, MD. August, 1987.

Publications (cont'd)

Herning, R.I., Pickworth, W.B., Glover, B., Richards, L. and Arnold, P.: The effects of atropine on electrophysiological indices of cognitive information processing. Sixth Chemical Reference Bioscience Review, The Johns Hopkins University Applied Physics Laboratory, Columbia, MD, August, 1987.

Pickworth, W.B. and Herning, R.I.: Diazepam effects on the spontaneous electroencephalogram (EEG) and evoked potentials in humans. Committee on Problems of Drug Dependence, NIDA Research Monograph Series, 1987, In press.

London, E.D., Broussolle, E., Links, J., Wong, D.F., Dannals, R.F., Wagner, H.N., Rippetoe, L.R., Holicky, B., Herning, R.I., Pickworth, W.B., Snyder, F.R., Cascella, N.G., Toung, J.K.T., Margolin, R.A. and Jaffe, J.H.: Human opioid abusers show regional decreases in cerebral glucose utilization during morphine euphoria. Soc. Neuroscience, 1987, In press.

Pickworth, W.B., Herning, R.I., Higgins, S.T., DeBorja, J. and White, B.: Atropine effects on spontaneous electroencephalogram (EEG) performance and instrumental estimates of vigilance in humans. Soc. Neuroscience, 1987, In press.

Herning, R.I., Pickworth, W.B., Glover, B., Richards, L., Kumor, K., Sherer, M. and Jaffe, J.H.: The effects of cocaine on information processing in heavy cocaine users. Committee on Problems of Drug Dependence, NIDA Research Monograph Series, 1987, In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00001-02 PVL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Validity of Laboratory Measures of Aggression

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.H. Jaffe	Acting Chief	PVL, ARC, NIDA
Others:	D. Fishbein	Staff Fellow	PVL, ARC, NIDA
	C. Muntaner	Visiting Fellow	PVL, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Psychology of Vulnerability Laboratory, Psychopathology & Cognitive Studies Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Motivation Assessment Battery (MAB) is a computerized laboratory game designed to provide subjects with the opportunity to aggress. Subjects are seated before a video display terminal where they are instructed that they can earn money for particular responses. An ostensible partner extracts money from them as they play and subjects have the ability to extract money from their "partner". Their responses are monitored to determine whether they can be characterized as aggressive or impulsive.

At present, approximately 80 subjects have been tested on this procedure during the discharge phase from the clinical ward. Their responses have been coded and entered into the central database of the Psychopathology Branch. Preliminary comparisons of these responses with other psychological and psychiatric measures collected during admission have been made. These analyses indicate that responses to provocation during the MAB are related to other psychological and psychiatric constructs. Further analyses will be conducted to assess the relationship of MAB measures to physiological and biological measures collected during separate protocols. Plans are to continue to test subjects on the MAB until data analysis procedures determine that the N is sufficient.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA00002-02 PVL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Serotonergic Stimulation on Neuroendocrine Measures in Aggressive Addicts

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.H. Jaffe	Acting Chief	PVL, ARC, NIDA
Others:	D. Fishbein	Staff Fellow	PVL, ARC, NIDA
	D. Lozovsky	Visiting Scientist	BVL, ARC, NIDA
	R. Herning	Acting Chief	CHP, ARC, NIDA
	W. Pickworth	Pharmacologist	CHP, ARC, NIDA

COOPERATING UNITS *(if any)*

Biology of Vulnerability Laboratory, Clinical Biology Branch
Cognitive Studies & Human Performance Lab, Psychopathology & Cognitive Studies

LAB/BRANCH

Psychology of Vulnerability Laboratory, Psychopathology & Cognitive Studies Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	1.0	2.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This study examines central serotonergic systems in drug addicts with low and high levels of aggressiveness as compared to normal volunteers by evaluating their neuroendocrine and behavioral responses to fenfluramine-induced serotoninergic stimulation. In addition, a glucose tolerance test (GTT) was included to assess blood glucose, insulin and other hormone levels known to be regulated by serotoninergic systems.

Data for 25 subjects have been analyzed and two papers are in preparation. Results indicate that high aggressive subjects have higher levels of prolactin as taken during 5 separate baseline periods. When adjusted for baseline, PRL and cortisol responses 3 and 4 hours after fenfluramine were significantly elevated in subjects with higher measures of aggressivity. In the GTT, high aggressive subjects showed a diminished prolactin response to glucose challenge and an exaggerated cortisol response. When the data were reanalyzed based on high and low impulsivity scores, group differences and correlation relationships became more pronounced for these neuroendocrine measures.

The study is in a continuation phase. Subjects are being tested with one fenfluramine trial and the GTT, excluding the second fenfluramine day and placebo. We are presently selecting those subjects with more extreme scores on aggression and impulsivity from normal and prisoner populations. In addition, current plans are to obtain spinal fluid to provide additional information on central serotonergic responses.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00003-02 PVL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Psychological, Behavioral, & Electrophysiological Markers of Antisocial Behavior

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.H. Jaffe	Acting Chief	PVL, ARC, NIDA
Others:	D. Fishbein	Staff Fellow	PVL, ARC, NIDA
	R. Herning	Acting Chief	CHP, ARC, NIDA
	J. Hickey	Social Scientist	EIL, ARC, NIDA
	W. Pickworth	Pharmacologist	CHP, ARC, NIDA
	C. Haertzen	Research Psychologist	BDL, ARC, NIDA

COOPERATING UNITS *(if any)*

Cognitive Studies & Human Performance, Psychopathology & Early Intervention
Early Intervention Lab, Psychopathology & Early Intervention Branch
Biology of Dependence Lab, Clinical Biology Branch

LAB/BRANCH

Psychology of Vulnerability Lab, Psychopathology & Early Intervention Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	1.5	1.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This study examines all subjects that enter the inpatient clinical ward. Upon entry, an "admissions" battery is administered including psychiatric diagnostic interview, psychological tests, behavioral measures of aggression and psychopathy, and an electrophysiological test battery. Results from these tests are continuously entered into the central database for analyses to be conducted. Several EEG and evoked potential measures have been shown to be related to psychological and behavioral test scores. In particular, slowing of the EEG and delayed auditory brainstem waves were found in individuals with high aggression measures.

Baseline EEG and EP's have been discontinued. Data analyses will continue until initial hypotheses have been tested.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00004-02 PVL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Assessment of an Instrument to Measure Alcohol-Related Behaviors

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.H. Jaffe	Acting Chief	PVL, ARC, NIDA
Others:	D. Fishbein	Staff Fellow	PVL, ARC, NIDA
	F. Snyder	Database Manager	CHP, ARC, NIDA
	C. Haertzen	Research Psychologist	BDL, ARC, NIDA
	J. Hickey	Social Scientist	EIL, ARC, NIDA
	C. Muntaner	Visiting Fellow	PVL, ARC, NIDA

COOPERATING UNITS *(if any)*

Cognitive Studies & Human Performance, Psychopathology & Cognitive Studies
Biology of Dependence Lab, Clinical Biology Branch
Early Intervention Lab, Treatment & Early Intervention Branch

LAB/BRANCH

Psychology of Vulnerability Lab, Psychopathology & Cognitive Studies Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this study was to assess the reliability and validity of the Alcohol-Related Behavior Questionnaire (ARBQ) developed at the Addiction Research Center, NIDA. The questionnaire is designed to determine types of behaviors which are associated with drinking and non-drinking conditions among individuals prone to substance abuse and those without histories of abuse. At present, the ARBQ has been discontinued and data from the test have been analyzed. The ARBQ scales were shown to have acceptable levels of reliability. A number of significant associations was found between scales on other personality measures of psychopathology and aggression, further validating the ARBQ. The overall findings suggest that both drinkers and non-drinkers are prone to disordered behavior with increasing levels of alcohol. It appears from the data that aggressive and/or depressive individuals drink more heavily initially which, in turn, triggers pre-existing aggressive mechanisms. A paper detailing these results is presently in final stages.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00005-02 PVL

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Aggression Among Drug Users and Normal Controls as a Function of Early Experience

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.H. Jaffe	Acting Chief	PVL, ARC, NIDA
Others:	C. Haertzen	Research Psychologist	BDL, ARC, NIDA
	D. Fishbein	Staff Fellow	PVL, ARC, NIDA
	C. Muntaner	Visiting Fellow	PVL, ARC, NIDA
	J. Hickey	Social Scientist	EIL, ARC, NIDA
	F. Snyder	Database Manager	CHP, ARC, NIDA

COOPERATING UNITS *(if any)*

Biology of Dependence Lab, Clinical Biology Branch
Early Intervention Lab, Treatment and Early Intervention Branch
Cognitive Studies & Human Performance Lab, Psychopathology & Cognitive Studies

LAB/BRANCH

Psychology of Vulnerability Lab, Psychopathology & Cognitive Studies Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Early Experience Questionnaire (EEQ) assesses aggressive, antisocial and conduct disorder behaviors manifested before the age of 12. Subjects completed this test during admission procedures and analyses were performed to determine its reliability and validity in order to compare test scores with previously obtained scores from other populations (i.e., hospitalized alcoholics), and to assess the independent contribution of early aggression in contrast to antisocial personality disorder (ASP) with the prediction of present aggression and psychopathology. The EEQ was found to have acceptable levels of reliability and validity. In addition, it was associated with more variables measuring hostility than was ASP personality diagnosis. The EEQ may reflect conditions that overlap with ASP but has independent value in the prediction of psychopathology and the onset of drug abuse behavior.

Due to the potential value of the EEQ in predicting the development of adult psychopathology and drug abuse from early childhood behaviors, the EEQ has been expanded significantly to reflect additional features of conduct disorder, hyperactivity, attentional deficit disorder and other problems. It is presently being administered to all subjects admitted to the research ward.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA02001-02 CHP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Mapping the Effects of Opioid Agonists by PET and EEG

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: R.I. Herning	Acting Chief	CHP, NIDA
Others: W.B. Pickworth	Scientist	CHP, NIDA

COOPERATING UNITS *(if any)*

The Neuropharmacology Laboratory (E.D. London)
The Johns Hopkins Hospital (D. Wong)

LAB/BRANCH

Cognitive Studies and Human Performance Laboratory

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Effects of morphine on the scalp EEG and FDG PET scans are being compared to determine the brain areas invoked in euphoria. The Cognitive Studies and Human Performance Laboratory is collecting and analyzing the EEG data from 20 scalp locations from post-addicts receiving placebo, 15 and 30 mg injections of morphine. These subjects subsequently received FDG PET scans while receiving placebo and 30 mg of morphine. The PET scans are performed by collaborators. The EEG data by itself provides insight into time course of electrophysiologic effects of a mu agonist in humans and the cortical distribution of mu effects. PET techniques do not by themselves provide information about the time course of the mu effects. The EEG and PET data together will help delineate the anatomical mechanisms involved in euphoria in humans.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA02101-03 CHP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Acute Abstinence From Tobacco: Electrophysiological and Cognitive Signs

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.E. Henningfield	Chief	BDL, NIDA
Others:	W.B. Pickworth	Scientist	CHP, NIDA
	R.I. Herning	Acting Chief	CHP, NIDA
	F. Snyder	Scientist	CHP, NIDA

COOPERATING UNITS *(if any)*

Biology of Dependence Lab (J. Henningfield, R. Nemeth-Coslett)

LAB/BRANCH

Cognitive Studies and Human Performance Laboratory

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Laboratory's efforts were directed toward the quantification of the cognitive and performance deficits during nicotine withdrawal and the treatment of these deficits with nicotine chewing gum. The EEG and cognitive function were monitored during a ten day period of tobacco withdrawal in heavy smokers. Some of the changes persisted over the entire ten day deprivation period. These measures included EEG alpha frequency, theta power, performance on selected cognitive tasks (especially a rapid arithmetic task) and a cognitive event related potential measure (N100 amplitude). Stimulus evaluation time, as measured by P300 latency, and the depth of stimulus evaluation battery were affected early during the tobacco deprivation period, but returned to smoking levels later during the deprivation period. Thus, the cognitive deficits are clearly apparent during abstinence from tobacco and contribute to relapse during treatment. The deficits during withdrawal have at least two different components-one affecting stimulus evaluation which dissipates after 5 to 7 days of abstinence and one affecting attention accompanied by lower arousal which persists ten days or longer. During this fiscal year these data were analyzed and are being prepared for publication.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA02811-02 CHP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Human Electrophysiology of Sigma Opiate Agonist

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.H. Jaffe	Director	ARC, NIDA
	R.I. Herning	Acting Chief	CHP, NIDA
Others:	W.B. Pickworth	Scientist	CHP, NIDA
	K. Kumor	Scientist	BVL, NIDA

COOPERATING UNITS *(if any)*

Biology of Vulnerability (J. Jaffe, K. Kumor)
University of Maryland, School of Pharmacy (N. Khazan, G. Young)

LAB/BRANCH

Cognitive Studies and Human Performance Laboratory

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Five subjects have been tested in a dosing paradigm designed to stimulate the sigma receptor in humans. A specific combination of pentazocine and naloxone, which blocks the kappa effect of pentazocine, produces a specific pattern of human EEG (2 Hz spectral peak) which appears to be generated by sigma receptor stimulation. Further subject testing and data analysis are needed before the publication of these EEG findings. The effects of sigma receptor stimulation on information processing is being evaluated. Clarification of the specific sigma subjective effects by a variety of questionnaires and interviews is also underway.

GPO 814-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA03101-02 CHP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effects of Atropine on Cognitive Information Processing

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.E. Henningfield	Chief	BDP, NIDA
Others:	W.B. Pickworth	Scientist	CHP, NIDA
	R.I. Herning	Acting Chief	CHP, NIDA
	F. Snyder	Scientist	CHP, NIDA

COOPERATING UNITS *(if any)*

Biology of Dependence Lab (J. Henningfield, R. Lamb)

LAB/BRANCH

Cognitive Studies and Human Performance Laboratory

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.6	0.6	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

An extensive battery of sensory and cognitive electrophysiological tasks is used to assess sensory, cognitive and performance deficity produced by atropine. The tasks include eyes open and eyes closed EEG, brainstem auditory evoked response, pattern reversal visual evoked response, the auditory rare event monitoring task, auditory continuous performance task and Sternberg auditory memory task (both immediate and delayed). Each of four doses of atropine (0, 2, 4, and 6 mg/70 kg) is investigated on two occasions. Eight subjects have been tested on these procedures and data are currently being analyzed.

The purpose of the study is to better understand the effects of cholinergic agents on cognition and performance; in particular, where in the information processing sequence atropine exerts its effects.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA03111-02 CHP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effects of Benzodiazepines on Cognitive Information Processing

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	R.I. Herning	Acting Chief	CHP, NIDA
Others:	W.B. Pickworth	Scientist	CHP, NIDA
	F. Snyder	Scientist	CHP, NIDA

COOPERATING UNITS *(if any)*

Biology of Dependence Laboratory (J. Henningfield, J. Roache, R. Lamb)

LAB/BRANCH

Cognitive Studies and Human Performance Laboratory

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.6	0.6	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

An extensive battery of sensory and cognitive electrophysiological tasks was used to assess sensory, cognitive and performance deficits produced by diazepam. The tasks include eyes open and eyes closed EEG, brainstem auditory evoked response, pattern reversal visual evoked response, auditory rare event monitoring task, the auditory continuous performance task and the Sternberg memory task (both immediate and delayed). Six doses (0, 2.5, 5.0, 10.0, 20.0 and 40.0 mg) of diazepam were used. Nine subjects were tested and the data are currently being analyzed.

The purpose of the study was to determine where in the information processing sequence the benzodiazepines exert their effects. Memory deficits have been previously noted, but it is yet unclear whether the deficit is due to poor encoding of the information or loss of the newly formed memory trace. The study is important in understanding the ways in which drugs of this class impair functioning.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA05801-01 CHP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Mapping the Effects of Cocaine by PET

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: R.I. Herning	Acting Chief	CHP, NIDA
Others: W.B. Pickworth	Scientist	CHP, NIDA

COOPERATING UNITS *(if any)*

Neuropharmacology Lab (E.D. London)
The Johns Hopkins Hospital (D.F. Wong)

LAB/BRANCH

Cognitive Studies and Human Performance Laboratory

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The effects of cocaine on scalp EEG and FDG PET scans are being compared to determine the brain areas involved in the cocaine-induced euphoria. In previous studies, cocaine increased EEG beta power. The distribution of cortical areas responsible for the EEG beta increase and the time course of the beta increase have not as yet been determined. The present study was designed to answer these two questions.

The complimentary nature of the EEG and PET data will delineate the anatomical and electrophysiologic mechanisms involved in cocaine induced euphoria.

In the previous studies which correlated EEG and PET-FDG studies of opioid euphoria, the EEG and PET studies of opioids were done on consecutive days. In the present study, EEG equipment has been transported to the site of PET scanner and EEG/PET studies are carried out concurrently.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA05901-01 CHP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cholinergic Pharmacology: Cognitive and Neurophysiologic Screen

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: R.I. Herning	Acting Chief	CHP, NIDA
Others: W.B. Pickworth	Scientist	CHP, NIDA

COOPERATING UNITS *(if any)*

Biology of Dependence Lab (J. Henningfield, J. Roache)

LAB/BRANCH

Cognitive Studies and Human Performance Laboratory

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.4	0.4	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A battery of tasks is being used to assess sensory, cognitive, and motor deficits produced by physostigmine. The tasks (eyes open EEG, physiological tremor, pattern reversal visual evoked response, self-paced motor potential, rare event monitoring, and Sternburg tasks) were designed to test neurophysiological indices of brain processing as well as behavioral performance. Sensory and cognitive performance was tested after both placebo or methscopolamine pretreatment. The pretreatment with methscopolamine tests whether the performance deficit was due to perpherial effects of physostigmine.

The purpose of the study is to better understand the effects of cholinergic agents on sensory, motor and cognitive performance at the neurophysiological level. Cholinesterase inhibitors are commonly used biological warfare agents. Techniques for determining the cognitive impairments produced by anticholinergics and safe models for inducing cholinergic stimulation are important steps in developing useful and effective antidotes to cholinesterase inhibitors.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA06201-01 CHP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Buprenorphine Maintenance & Withdrawal on Cognitive & Neurophysiologic Measures

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	R.I. Herning	Acting Chief	CHP, NIDA
Others:	W.B. Pickworth	Scientist	CHP, NIDA
	F. Synder	Scientist	CHP, NIDA

COOPERATING UNITS *(if any)*

Research Support Branch (R.E. Johnson, P.J. Fudala)
Early Intervention Branch (B. Brown, W. Weddington)

LAB/BRANCH

Cognitive Studies and Human Performance Laboratory

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.8	0.8	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Buprenorphine is being evaluated as a new agent for detoxification and maintenance in the treatment of heroin addiction. As part of an extensive series of tests, the effects of buprenorphine maintenance and subsequent buprenorphine withdrawal are being investigated in heroin users who were switched to buprenorphine. After being maintained on buprenorphine daily or every other day by sublingual dosing, the addicts are abruptly withdrawn from buprenorphine. Various aspects of cognition are measured using a battery of cognitive tasks throughout the maintenance and withdrawal phases. In some of the tasks, neurophysiologic measures of cognitive information processing supplemented the behavioral measures of cognitive performance. Pupil size and the pupillary light reflex are also measured. The effects of the two dose conditions on cognitive processing will be compared. Likewise, the effects of abrupt buprenorphine withdrawal on cognition will be evaluated. Pupil measures were included because of their sensitivity to opiate effects. Seven subjects have completed the protocol.

The specific aim of the cognitive testing is to determine whether there are severe cognitive deficits when addicts are dosed every other day with buprenorphine. The testing during withdrawal is designed to determine the extent and time course of cognitive disruption during buprenorphine withdrawal.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA06801-01 CHP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cognitive Neurophysiologic Signs of Cocaine Withdrawal

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: R.I. Herning	Acting Chief	CHP, NIDA
Others: W.B. Pickworth	Scientist	CHP, NIDA

COOPERATING UNITS *(if any)*

Early Intervention Branch (B. Brown, W. Weddington)

LAB/BRANCH

Cognitive Studies and Human Performance Laboratory

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.4	0.4	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Cognitive impairments and sleep disruption have been reported in patients withdrawing from cocaine. The nature of these disorders has yet to be documented in clinical laboratory studies. The present study evaluates cognitive information processing in subjects on a clinical ward withdrawing from cocaine with a battery of tasks (auditory rare event monitoring, complex visual rare event monitoring, Sternburg memory, visual motor tracking). Sleep quality and duration is monitored by a subjective questionnaire, wrist activity meters and sleep EEG recording. Seven subjects have been tested in this study over a one month withdrawal period.

Clarification of the nature of the cognitive deficits and of sleep loss may lead to more effective treatment strategies for cocaine withdrawal.

Treatment and Early Intervention Research Branch

Barry S. Brown, Ph.D., Chief

Introduction:

The Treatment and Early Intervention Research Branch was organized in September, 1986 to study the efficacy of treatment and early intervention strategies. The Branch conducts research regarding the efficacy of new psychopharmacologic and behavioral treatments for drug dependence, especially for cocaine and i.v. heroin use. In addition, the Branch explores the efficacy of strategies to prevent or reduce drug taking behavior among young people with high vulnerability for drug taking. Research is carried out on both the ARC inpatient unit and its recently completed outpatient unit. In addition, the Branch makes use of treatment facilities located in the Baltimore area. The Treatment and Early Intervention Research Branch is currently divided into two laboratories.

1. Clinical Trials Laboratory - Barry S. Brown, Ph.D., Chief

Overview

The Clinical Trials Laboratory is responsible for the conduct of studies assessing the efficacy of innovative treatment approaches. The interventions studied are primarily psychopharmacological and/or behavioral in type and are conducted in both inpatient and outpatient settings. Studies explore the efficacy of interventions with a view toward the replication of effective strategies by the service delivery community. Additional studies examine issues significant to the service delivery process.

These objectives are being pursued using a variety of research techniques, including (1) use of single-blind and double-blind procedures with pharmacologic interventions, (2) use of experimental design employing random assignment to control and/or comparison groups with psychosocial/behavioral interventions, and (3) obtaining and quantifying observational data to clarify behaviors significant to the conduct of drug abuse treatment.

Studies are frequently conducted in collaboration with other laboratories of the ARC and with cooperating facilities of the State of Maryland Drug Abuse Administration. Within the ARC, joint projects are being conducted in association with the Cognitive Studies and Human Performance Laboratory, the Psychology of Vulnerability Laboratory and the Chemistry and Drug Metabolism Laboratory. In addition, several programs of the Maryland Substance Abuse Authority Administration have indicated a willingness to join with the Branch as appropriate. Currently, the X-Cell and Man Alive programs are working with the Branch in studies of waiting list behaviors and of the use of psychopharmacologic strategies with methadone maintenance clients, respectively.

Long-term goals of the Clinical Trials Laboratory will continue to be the exploration and clarification of issues significant to the treatment process and the examination of interventions that have promise for service delivery. For the forseable future, concerns about the impact of AIDS on drug abuse treatment, concurrent psychiatric diagnoses issues, and the effort to provide effective treatment for cocaine abusers will likely remain dominant.

Summary Of Ongoing Research

A. Effects of Pharmacologic Agents on Cocaine Abuse Treatment: Weddington, W.W., Brown, B.S., Jaffe, J.H. and Rose, M.

Systematic investigation comparing different pharmacologic regimens for cocaine dependence with each other under blind conditions are only beginning to be reported in the literature. This study involves the comparison of desipramine hydrochloride and amantadine hydrochloride in regimens suggested as useful in earlier open-trial investigations.

An additional treatment group receives amantadine initially with a later change-over to desipramine in an effort to take advantage of the presumed pharmacologic action of each of those drugs. A fourth group receives placebo and then drug. The treatment regimen for the four randomly assigned groups lasts a 12-week period and involves twice weekly counseling in addition to daily medication.

The measures in this study assess cocaine craving, sleep satisfaction, mood, drug use, psychological symptoms, and depression on a weekly or more frequent basis. Reports of side effects, blood pressure and pulse are obtained three times weekly. In addition, bloods are drawn periodically to assess compliance with the therapeutic regimen. Counselors complete scales weekly to record psychological functioning. Followup will be made to assess clients' functioning six and twelve months after the completion of treatment.

The study may permit an assessment of two of the major pharmacologic strategies that have been suggested for use in outpatient treatment of cocaine abusers with comparison to a third strategy incorporating strengths of the two pharmacologic agents. Thorough initial psychological assessments will permit subsequent analysis of factors that predict high probability of drop-out or failure to improve. Given the increase in cocaine dependence, and in public concern about that drug, there is a particular urgency that attaches to studies designed to clarify treatment initiatives that may be useful in alleviating this problem.

B. Use of Pharmacologic Agents for Cocaine Dependence in Methadone Maintenance Clients: Weddington, W.W., Brown, B.S., Rose, M., and Jaffe, J.H.

Cocaine use has long been associated with opiate dependence and indeed the two drugs have been used together to achieve particular psychic states. Increasingly, there have been reports from methadone programs of significant levels of cocaine use by persons stabilized on methadone. Under double-blind conditions, this study explores the efficacy of amantadine hydrochloride, desipramine hydrochloride, and a placebo condition to determine the utility of the different pharmacologic regimens with cocaine dependent methadone clients. In this study, cocaine-dependent methadone maintenance clients in an area treatment program are randomly assigned to each of the three treatment groups described, and receive both methadone and the study-prescribed medication on a daily basis. Counseling and all other clinic activities are available to all four client groups.

The measures employed involve weekly or more frequent assessments of cocaine craving, sleep satisfaction, mood, psychological symptoms, depression and drug use. Reports of side effects as well as blood pressure and pulse are obtained three times per week. In addition, blood levels are obtained on a weekly basis for purposes of both safety and determination of treatment compliance. Counselors report both depression and overall psychological functioning on a once weekly basis, and assessment will be made of functioning post-treatment at 6 and 12 month intervals.

Clarification of the role which may be played by available pharmacologic agents in permitting clients to be retained in methadone treatment can be significant not only to the process of drug abuse rehabilitation, but to the containment of AIDS and HIV infection as well.

C. Behavioral and Physiological Effects Associated with Acute Cessation of Cocaine: Weddington, W.W., Cone, E., Dax, E., Herning, R.I. and Rose, M.

Cocaine cessation has been reported as leading to significant depressive symptoms with concomitant irritability, anxiety and sleep abnormality. These observations have been largely restricted to outpatient populations and the current investigation is intended to clarify behavioral and physiological functioning associated with the cessation of cocaine use under controlled, i.e., inpatient conditions.

Individuals meeting criteria for cocaine dependence are admitted for study lasting up to six weeks. Measures are made at prescribed intervals to assess cognitive performance, neuroendocrine functioning, cocaine and cocaine-metabolite excretion, psycho-

logical status, depressive ideation, drug craving, sleep satisfaction/dissatisfaction, and subjects' cardiovascular functioning. A particular concern in this study will be the clarification of both the extent of sleep disorder associated with cessation of cocaine use and the relationship of that disorder to other measures of psychobiologic functioning. Subjects will be available for followup assessments every other month up to one year post-discharge.

D. Characteristics of Waiting List Clients and Behaviors: Brown, B.S., Hickey, J.E., Jaffe, J.H.

In much of the country, programs report themselves to be maintaining lengthy waiting lists that delay, if they do not frustrate, entrance into drug abuse treatment. To date, no studies have been conducted that are designed to examine the behaviors of waiting list applicants with regard to prosocial/antisocial functioning, with regard to efforts to locate alternative treatment opportunities and/or regarding intentions to remain available to the treatment program initially contacted. It is apparent that the attitudes and behaviors of persons on a waiting list can have significance for their later program compliance and for their functioning in the community. Indeed, these concerns have been newly aroused by the threat of HIV infection posed by intravenous drug users.

This project involves drawing a stratified random sample of individuals who have placed themselves on the waiting list for an area residential drug abuse treatment program. The sample is stratified by gender and length of time on the waiting list. The measures in use are designed to clarify the demographics, background and psychological functioning of waiting list clients; to examine functioning in the community in regard to drug using, employment and antisocial activities; to assess subjects' efforts to obtain drug abuse treatment; and their risk taking/risk reduction behaviors in relationship to HIV infection. In addition, the study seeks to explore issues in terms of community pressures for and against entry into treatment.

Study of the behaviors of individuals who are awaiting entry into treatment can help clarify individuals' continuing accessibility to treatment programs, the cost, if any, to society in maintaining waiting lists, and can lay the groundwork for the development of strategies designed to permit clients to remain available to treatment programs. In addition, study will clarify the extent to which intravenous (i.v.) cocaine users are practicing risk reduction behaviors in relationship to HIV infection and the ways in which i.v. cocaine users have made efforts to modify risk-taking behaviors in association with the threat of AIDS.

E. Opioid Dependence: Pharmacological Study of Buprenorphine: Johnson, R.E., Fudala, P.J., Dax, E., Cone, E., Herning, R., et al.

Buprenorphine is a partial agonist of the morphine type with an analgesic potency 25-50 times that of morphine. Buprenorphine produces: subjective effects acceptable to opioid abusers; a duration of physiological and subjective effects similar to methadone; and blockade of exogenously administered opiates. Studies assessing buprenorphine's effects on opioid self-administration and use in detoxifying opioid addicts have been positive.

The use of illicit i.v. drugs has been correlated with the AIDS epidemic. In order to decrease illicit i.v. drug use, additional interventions for opioid addicts are needed. It has been shown that many opioid addicts refuse to seek treatment due to the limited chemotherapeutic interventions available to clinicians. Given this refusal by many addicts, the development of alternative therapeutic interventions seems most appropriate and necessary.

This study is designed to assess the pharmacodynamic and pharmacokinetic properties of buprenorphine in controlled inpatient and outpatient trials. This study will assess (1) a rapid dose induction procedure, (2) the clinical efficacy of different dose regimens, (3) the duration of effective blockade, and (4) withdrawal from different dose regimens. Twelve subjects will be studied in each dose regimen group using a battery of subjective, physiological, cognitive, kinetic, neurohormonal and electro-physiological measures.

Data collected through this study should add to the basic clinical knowledge presently available for using buprenorphine with an opioid dependent population.

Publications for FY - 1987

Brown, B.S.: Networking between research and service delivery. Inter. J. Addictions 22: 301-317, 1987.

Brown, B.S., Buhringer, G., Kaplan, C.D. and Platt, J.J.: German/American report on the effective use of pressure in the treatment of drug addiction. Psychol. Addict. Behav. 1: 38-54, 1987.

Platt, J.J., Buhringer, G., Kaplan, C.D., Brown, B.S., and Taube, D.O.: The prospects and limitations of compulsory treatment for drug addiction: Results of a German-American workshop. J. Drug Issues, In press.

Brown, B.S.: Civil commitment - International issues. NIDA Research Monograph Series, In press.

Brown, B.S.: Compelling entrance into drug abuse treatment. J. Drug Issues, In press.

Brown, B.S. and Beschner, G.M.: AIDS and HIV infection - Implications for drug abuse treatment. J. Drug Issues, In press.

Brown, B.S.: Contributions of the DARP to Treatment Research Methods and Policy. In: Applications of Interactionist Psychology. New York, Earlbaum Press, In press.

Brown, B.S.: The Emerging Mainstreaming of Drug Abuse Treatment. In: Treating the Drug User: Selected Planning Models, Issues, Parameters and Programs. Geneva, Switzerland, Sandoz, 1986.

2. Early Intervention Laboratory - Barry S. Brown, Acting Chief

Overview

The Early Intervention Laboratory is responsible for the conduct of study designed to clarify the efficacy of interventions especially targeted to adolescents and preadolescents who are high risk for drug taking behaviors. A concern in the studies undertaken is to clarify the utility of interventions for use with young persons whose drug taking behaviors have resulted, or threaten to result, in family and community conflict. Focus is also placed on psychobiological issues of substance abuse and dependence, and on issues significant to the development of effective prevention programming.

The objectives being pursued make use of a variety of study procedures, including (1) experimental research design involving random assignment to control and/or comparison groups for purposes of clarifying the efficacy of early interventions or preventive strategies; (2) use of structured interview schedules designed to clarify issues in the development of drug taking behaviors; and (3) the use of psychobiologic assessment to study the development of drug-taking behaviors and to clarify differences between vulnerable and less vulnerable populations. In the conduct of its research the Laboratory has allied itself with additional laboratories of the Addiction Research Center, most notably the Psychology of Vulnerability Lab and the Cognitive Studies and Human Performance Lab. In addition, the Laboratory is working with adolescent treatment programs associated with the Maryland Substance Abuse Administration and the Maryland Juvenile Services Administration.

The long-term goals of the Early Intervention Research Branch are to explore the efficacy of early intervention strategies designed to contain young persons' deepening involvement in substance abuse and to clarify etiologic issues in the development of substance abuse. A particular emphasis has been placed on clarifying the relationship between the development of drug using behaviors and those behaviors associated with aggressive conduct disorders. Issues of the extent to which learning disorder and early school failure contribute to the development of substance abusing and other antisocial behaviors similarly require further clarification.

Summary of Ongoing Research

A. Family Intervention with Young Chronic Cocaine Abusers: Rose, M., Weddington, W.W., Brown, B.S. and Jaffe, J.H.

There is increasing interest in the use of family therapy in drug abuse, in particular with youthful substance abusers. At the same time, technological advances have made it possible for parents and others to monitor and help contain drug taking behaviors. Study has been initiated to examine the utility of traditional family therapy, in which the substance abuse is viewed as a symptom of family disruption, with a family therapy strategy that permits parents to monitor drug use by their adolescents in treatment (using toxicologic findings) and to permit drug use to be made the primary focus of family treatment. Given the particular significance of cocaine use among young people, the study focus has been placed on treatment of youthful cocaine users.

Youthful cocaine users and one or more family members are randomly assigned to groups providing either traditional family therapy or family therapy/drug use monitoring. Treatment is designed to last a period of 24 weeks with twice weekly sessions (1 family and 1 individual) for the length of that period. Counselors follow a standard regimen of family therapy differing only in the use of urine toxicologies. Measures are obtained pre-treatment, post-treatment and at 6 and 12 month intervals after treatment has been completed. The measures assess substance abuse, psychological functioning, family functioning, impulse control and aggressivity, and school-based performance. Pre-post-assessments are also made of parents using measures of family functioning.

B. Spread of Cocaine Use: Hickey, J.E. and Brown, B.S.

Spread of cocaine use through both adolescent and adult communities has given rise to widespread concern and a considerable investment of resources in an effort at containment of that spread. Nonetheless, little is known of the way in which cocaine use has spread in the community and the extent to which issues in the spread of cocaine differ for adults and adolescents. In addition, in spite of considerable effort to develop prevention programming, little is known with regard to concerns about cocaine in vulnerable

populations or regarding the sources of information that are available to those populations and seen by them as being credible. This investigation examines issues in the initiation into cocaine use of young people and their older peers as well as an examination of available sources of information about cocaine and the relative credibility attached to those sources.

The project involves drawing samples of adolescents and adults in treatment for cocaine abuse. A structured interview schedule is used with subjects designed to determine the histories of their drug taking and, specifically, cocaine-using behaviors; involvement in initiating others to cocaine use; experiences with regard to cocaine use and other drug use in their peer groups, etc. Using 10 centimeter analogs, the study also explores ratings of availability and credibility of information sources with regard to cocaine use and the significance attached to the several types of risks seen as consequent to cocaine use.

Publications for FY - 1987

Brown, B.S. and Mills, A.: At-Risk Youth: Four Populations, NIDA Research Monograph Series, In press.

Johnson, J.L., Adinoff, B., Bisserbe, J.C., Matin, P., Rio, D., Rohrbaugh, J.W., Zubovic, E.A. and Eckardt, M.J.: Brain imaging in organic brain syndromes associated with positron emission tomography. Alcohol.: Clin. Exp. Res. 10: 237-240, 1986.

Johnson, J.L., Rolf, J.E. and Rebeta, J.L.: Assessment of Brain Functioning in Individuals at Biosocial Risk: Examples from Alcoholic Families. In A. Petersen (Ed.): Brain and Behavioral Development: Biosocial Perspectives, In press.

Johnson, J. and Bennett, L.: School-aged Children of Alcoholics: Theory and Research, In press.

Johnson, J.: Issues in brain imaging. Br. J. Addict., In press.

Rolf, J. and Johnson, J.: Protected or Vulnerable: AIDS Challenge to Developmental Psychopathology. In J. Rolf, D. Cicchetti, K. Neuchterlein, S. Weintraub (Eds.): Risk and Protective Factors in the Development of Psychopathology, In press.

Johnson, J., Rolf, J. and Isreael, E.: Cognitive and academic performance in children of alcoholics. Br. J. Addict., In press.

Publications (cont'd)

Rolf, J. and Johnson, J.: Depressive affect in children of alcoholics. Br. J. Addict., In press.

Semple, W.E., Johnson, J., Cohen, R., King, A.C., Nordahl, T., Gross, M. and Cappelletti, J.: Inter-rater reliability in positron emmission tomography image analysis, Submitted.

Johnson, J., Bennett, J., Wolin, S. and Eckardt, M.: Cognitive performance patterns of children from alcoholic and nonalcoholic families, Submitted.

Organizations Collaborating with the Treatment and Early Intervention Research Branch

Maryland Substance Abuse Administration, Baltimore, Maryland

Taylor-Manor Hospital, Ellicott City, Maryland

Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia

Department of Psychiatry, Medical School of the University of Maryland, Baltimore, Maryland

Psychiatry Department, University of Miami Medical School, Miami, Florida

The Johns Hopkins University, Baltimore, Maryland

Maryland Juvenile Services Administration, Baltimore, Maryland

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00001-01 TEI

PERIOD COVERED

June 1, 1987 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Physiological and Psychological Aspects of Cocaine Cessation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	W.W. Weddington	Visiting Scientist	Clinical Trials
Others:	E. Dax	Chief	AIDS, NIDA
	R.I. Herning	Chief	CHP, NIDA
	E. Cone	Chief	CDM, NIDA

COOPERATING UNITS *(if any)*

Chemistry and Drug Metabolism Lab, Cognitive Studies and Human Performance Laboratory, AIDS Lab

LAB/BRANCH

Clinical Trials Laboratory

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.65	0.25	0.40

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unraduced type. Do not exceed the spece provided.)*

This study examines behavioral and physiological aspects associated with the cessation of cocaine abuse by humans and provides longitudinal data regarding the psychological and physiological aspects of abstinence from cocaine. Specifically, craving for cocaine was examined as were changes in mood, cardiovascular function, sleep, cognition, neuroendocrine function and excretion of cocaine and cocaine-metabolites in urine and saliva by persons who abruptly stop abusing cocaine after they are admitted to a research unit.

Up to 20 persons will be admitted to the study and measures will be obtained for up to 6 weeks. Subjects will be re-evaluated every other month up to a year regarding relapse and abstinence phenomena.

To date, seven subjects have been admitted and three have completed the inpatient component. Preliminary findings suggest impaired cognition which improves rapidly during the first ten days, a uniform pattern of cocaine and cocaine metabolite excretion, and a uniform pattern of initial sleep disturbance. Our preliminary findings also suggest suppression of the diurnal rhythm of prolactin, although cortisol diurnal rhythm is maintained.

The significance of this project lies in the determination of phenomena associated with cocaine cessation, or "withdrawal" from cocaine.

PHS 6040 (Rev. 1/84)

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00002-01 TEI

PERIOD COVERED

June 1, 1987 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Placebo Controlled Trial of Amantadine & Desipramine for Cocaine Abuse

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	W.W. Weddington	Visiting Scientist	Clinical Trials
Others:	M. Rose	Social Worker	EI, NIDA
	B.S. Brown	Chief	TEI, NIDA
	J.H. Jaffe	Director	ARC, NIDA

COOPERATING UNITS *(if any)*

Clinical Trials Laboratory

LAB/BRANCH

SECTION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

INSTITUTE AND LOCATION

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.90	0.25	2.65

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this study is to examine longitudinal behavioral and physiological aspects regarding cessation of cocaine abuse by human subjects enrolled in an outpatient treatment program and to examine the efficacy of two drugs, amantadine and desipramine, to assist individuals who are stopping cocaine abuse. Up to 80 patients will be enrolled in this study and receive counseling and medication or placebo for 12 weeks. Craving for cocaine, mood states, substance use/abuse, urine toxicology, serum drug levels, and abstinence among four treatment groups will be examined: (1) 3.5 weeks of amantadine followed by 8.5 weeks of placebo; (2) 3.5 weeks of amantadine followed by 8.5 weeks of desipramine, (3) 12 weeks of desipramine; and (4) 12 weeks of placebo.

To date, 30 patients have begun treatment. Preliminary data suggest 90% attendance among clients retained in program, 25% drop-out rate by week 6, and few medication side effects.

The significance of this study is an evaluation of the efficacy of two medications which are proposed to assist cocaine abusers and an assessment of psychological and physiological phenomena associated with cocaine cessation.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00003-01 TEI

PERIOD COVERED

May 1, 1987 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Characteristics of Waiting List Clients and Behaviors

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: B.S. Brown	Chief	TEI, NIDA
Others: J. Hickey	Social Worker	EI, NIDA

COOPERATING UNITS *(if any)*

Maryland Substance Abuse Administration (X-Cell Program)

LAB/BRANCH

Clinical Trials Laboratory

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.50	0.25	0.25

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Programs in many parts of the country are reporting lengthy waiting lists for entry into drug abuse treatment. The effect on people's behavior about the process of thinking of being on a waiting list is unknown. This study is exploring the waiting list behaviors of persons who have registered for treatment at one area cocaine abuse treatment program. A random sample of 60 applicants for treatment, stratified by gender and length of time on the waiting list, has been drawn. An interview schedule has been developed for use with subjects which explores drug and alcohol use, antisocial and prosocial behaviors, relations with friends and family, efforts to locate other treatment resources, satisfaction with self, and future expectations during the waiting list period. In addition, exploration is being made of both psychological symptoms and AIDS-related risk taking/risk reducing behaviors.

Study findings should clarify whether and to what extent clients modify drug-taking and other behaviors of concern consequent to placing themselves on waiting lists to enter treatment. In addition, it may permit an understanding of AIDS-related risk taking behaviors in a sample of i.v. cocaine users.

GPO 814-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00004-01 TEI

PERIOD COVERED

August 1, 1987 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cocaine Abuse Treatment for Clients Receiving Methadone Maintenance

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	W.W. Weddington	Visiting Scientist	CT, NIDA
Others:	B.S. Brown	Chief	TEI, NIDA
	M. Rose	Social Worker	EI, NIDA
	J.H. Jaffe	Director	ARC, NIDA

COOPERATING UNITS *(if any)*

Maryland Substance Abuse Administration (Man Alive Program), The Johns Hopkins University (Francis Scott Key Medical Center)

LAB/BRANCH

Clinical Trials Laboratory

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.85	0.25	1.60

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Methadone programs are reporting significant numbers of clients remaining opiate-free while becoming involved in continuing patterns of cocaine abuse. The purpose of this study is to assess the efficacy of pharmacologic adjuncts to methadone maintenance treatment in regimens that have been suggested as being useful in earlier work with cocaine abuse clients. In double-blind study, methadone maintenance clients showing urine toxicologies consistently positive for cocaine over a period of at least two months will be randomly assigned to one of four medication groups: desipramine hydrochloride, amantadine hydrochloride, amantadine followed sequentially by desipramine, and placebo. A total of 20 subjects in each cell is contemplated. The intervention will last a total of 12 weeks. Measures will be taken of drug use, client mood, psychological symptoms, depressive functioning, drug craving, sleep satisfaction, and reported drug effects using a repeated measures design. In addition, there will be follow-up of clients 6 and 12 months post-treatment. Study findings can be expected to have significance for efforts to successfully treat opiate clients and thereby may have importance for efforts to contain the spread of HIV infection as well.

GPO 814-818

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00005-01 TEI

PERIOD COVERED

April 1, 1987 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Spread of Cocaine in Adult and Adolescent Populations

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: J. Hickey	Social Worker	EI, NIDA
Others: B.S. Brown	Chief	TEI, NIDA

COOPERATING UNITS *(if any)*

Maryland Substance Abuse Administration (Epoch Counseling Centers, X-Cell Program)

LAB/BRANCH

Early Intervention Laboratory

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.50	0.25	0.25

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this study is to examine similarities and differences between samples of adult and youthful cocaine users in terms of the process of initiation into cocaine use, the course of involvement with cocaine, the initiation of others into cocaine use, the threats to self seen as posed by cocaine use, friendship and family relationships and the supports they offer for and against cocaine use, as well as sources of information about cocaine seen as available to the subject and the credibility attached to those information sources. Samples of 60 adults (26 and older) and 60 youths (21 and below) stratified by gender and ethnicity are drawn from area residential and outpatient programs. Structured closed-ended interview schedules assess issues in cocaine use as described above. In addition, information is obtained regarding relevant background and demographic characteristics. Data have been gathered on 56 subjects to date.

Study findings clarifying issues in the initiation of cocaine use, its spread to others, and the availability and credibility of information sources about cocaine should be useful to the development of early intervention and prevention efforts.

PHS 6040 (Rev. 1/84)

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00006-02 TEI

PERIOD COVERED

February 1, 1987 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Family Intervention with Young Chronic Cocaine Abusers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	M. Rose	Social Worker	EI, NIDA
Others:	B.S. Brown	Chief	TEI, NIDA
	J.H. Jaffe	Director	ARC, NIDA
	W.W. Weddington	Visiting Scientist	CT, NIDA

COOPERATING UNITS *(if any)*

Maryland Juvenile Services Administration

LAB/BRANCH

Early Intervention Laboratory

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.25	0.75

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this study is to examine the efficacy of traditional family therapy with a family therapy regimen making use of urine toxicology reports such that parents can monitor their adolescents' drug use. Forty adolescents and their families are being randomly assigned to one of two treatment conditions (family therapy with toxicology reports and family therapy only). Treatment lasts 24 weeks with twice weekly sessions (one family and one individual) in which trained counselors follow a standard regimen. Measures of substance abuse, psychological functioning, and family functioning are obtained pre-treatment, post-treatment, and at six and twelve month intervals after treatment has been completed.

To date, twenty families have been evaluated and eight have been admitted to treatment. It is hoped that findings from this study will clarify the benefits to family therapy, if any, of adding a capacity for routine monitoring of adolescents' drug use.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00007-01 TEI

PERIOD COVERED

April 1, 1987 to January 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Opioid Dependence Intervention: Pharmacologic Study of Buprenorphine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: R.E. Johnson

Others: P.J. Fudala
E.J. Cone
E. Dax
J.E. Henningfield
R.J. Herning
J.H. Jaffe
W.R. Lange
W.W. Weddington

COOPERATING UNITS *(if any)*

Research Support Branch, Chemistry & Drug Metabolism Lab, Neuroendocrine/ Immunology Lab, Biology of Dependence & Abuse Potential Assessment Lab, Cognitive Studies and Human Performance Lab, Clinical Trials Lab

LAB/BRANCH

Early Intervention and Treatment

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.4	1.9	3.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Buprenorphine is a partial agonist of the morphine type with an analgesic potency 25-50 times that of morphine. Buprenorphine produces: subjective effects acceptable to opioid abusers; a duration of physiological and subjective effects similar to methadone; and blockade of exogenously administered opiates. Studies assessing buprenorphine's effects on opioid self-administration and use in detoxifying opioid addicts have been positive.

The use of illicit i.v. drugs has been correlated with the AIDS epidemic. In order to decrease illicit i.v. drug use, additional interventions for opioid addicts are needed. It has been shown that many opioid addicts refuse to seek treatment due to the limited chemotherapeutic interventions available to clinicians. Given this refusal by many addicts, the development of alternative therapeutic interventions seems most appropriate and necessary.

This study is designed to assess the pharmacodynamic and pharmacokinetic properties of buprenorphine in controlled inpatient and outpatient trials. This study will assess (1) a rapid dose induction procedure, (2) the clinical efficacy of different dose regimens, (3) the duration of effective blockade; and (4) withdrawal from different dose regimens. Twelve subjects will be studied in each dose regimen group using a battery of subjective, physiological, cognitive, kinetic, neurohormonal and electrophysical measures.

Data collected through this study should add to the basic clinical knowledge presently available for using buprenorphine in an opioid dependent population.

PHS 6040 (Rev. 1/84)

GPO 914-918